Universitatea *Transilvania* din Braşov

HABILITATION THESIS

THERAPEUTIC APROACH IN SCHIZOPHRENIA-FROM DIAGNOSIS TO RECOVERY

Domain: MEDICINE

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LIST OF ABBREVIATIONS

DSM–IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision,
PANSS	Positive and Negative Schizophrenia Scale
CGI	Clinical Global Impression
GAF	Global Assessment of Functioning
FGA	First Generation Antipsychotic
SGA	Second Generation Antipsychotic
CLZ	Clozapine
GP	General Practitioner
LAIs	Long Acting Injectables
CBC	Complete Blood Count
CT	Computer Tomography
NMS	Neuroleptic Malignant Syndrome
PIS	Post Injection Syndrome
SD	Standard Deviation
HR	Hazard Ratio
SCD	Sudden Cardiac Death
TRS	Treatment Resistant Schizophrenia
FDA	The Food and Drug Administration
LBW	Low Birth Weight
EPS	Extrapyramidal Side-Effects
NMDA	N-Methyl-D-aspartate
SPC	Summary of Product Characteristics
TDM	Therapeutic Drug Monitoring
BEN	Benign Ethnic Neutropenia
CI	Confidence Interval
CAD	Coronary Artery Disease
SUD	Sudden Unexplained Death
CPR	Cardiopulmonary Resuscitation

OHCA	Out-of-Hospital Cardiac Arrest
NICE	National Institute for Health and Care Excellence
ID	Intellectual Disabilities

A. SUMMARY

I graduated from the Faculty of Medicine of the University „ Gr. T. Popa'' 'of Iasi in 1999 and I began my specialization in psychiatry in 2002 after residency contest. I worked uninterrupted in Hospital of Psychiatry and Neurology in Brasov initially as a resident from 2002 until 2007, then continuing as a specialist from 2007 to 2012. I became MD psychiatrist in 2012. In recognition of professionalism and organizational capacity I was was named Chief of Clinical 3rd Department in 2015. I am the Chairman of Ethics Committee and Board Member of Hospital Medical Council.

In 2002 I became a junior lecturer in psychiatry discipline competition at the Medical Faculty of the Transilvania University of Brasov. My academic career development was done by following the steps promoted competition: teaching assistant in 2009, lecturer in 2012 and associate professor in 2015.

In parallel with the clinical work I have carried out an intense research activity. I started and finished the doctoral thesis entitled „Correlations of somatosensory psychiatric and therapeutic clinical assessment and treatment of depressive disorders''. The aim, a real novelty at the time approached metabolic syndrome and it's implications in affective disorders.

I started my research activity clinical trials in 2002, as a member of the clinical trial team coordinated by Mrs. Prof. Univ. Dr. Victoria Burtea. I participated in the most important European study dedicated to the first episode of schizophrenia (EUFEST) led by the European Research Group of schizophrenia. The study primarily aimed to compare the efficacy and safety of treatment with atypical antipsychotics (amisulpride, quetiapine, olanzapine, zyprasidone) compared to haloperidol. The results of this study remain a landmark even after more than 10 years.

I participated as an investigator in more than 20 clinical trials that led to important molecules (SeroquelXR, Zypadhera, Asenapine, etc.) but also to calibrate for Romanian language of valuable assessment scales as PETIT, RDQ, NSI -16, RISA, etc.

I participated as principal investigator in MIN-103 clinical trial to specify efficacy and safety of new molecules for the treatment of schizophrenia.

Habilitation thesis is structured in the format required by the current rules. The thesis is the presentation of my professional activities, academic and research in 15 years.

The clinical activity in a psychiatric emergency department led to the development and publication of two major studies on rapid titration of clozapine in schizophrenia and bipolar disorder. Rapid titration of clozapine has aroused the attention of big names in the world like John M Kane, Christoph U Correll, Peter Manu who agreed to participate as authors in

publishing articles in **Acta Psychiatrica Scandinavica** and ***Journal of Affective Disorders***. Studies showed for the first time worldwide the efficiency and safety of clozapine titration rapid in patients with refractory bipolar I disorder.

Lives of patients with schizophrenia was one of the priorities of my research activity. Starting with the ethical aspects of depot antipsychotic treatment in the first episodes of psychosis and to the treatment of women with schizophrenia who become or want to become pregnant. So we published articles on antipsychotic treatment during pregnancy in patients with schizophrenia and aspects of involuntary hospitalization of these patients in ***Therapeutics and Clinical Risk Management*** and the ***American Journal of Therapeutics***.

Institutionalization of patients with schizophrenia was and still is a theme always present for family and society through the multitude of issues that are involved: ethical, moral, material, human. This traumatic event for the family and patient generate huge cost especially when institutionalized patitents are still young. We performed a study and published results in ***Revista de Cercetare si Interventie Sociala.***

Sudden death of hospitalized patients with schizophrenia, was another concern in research. We wanted to check if antipsychotic treatment may have an impact in these cases. The study we conducted showed that cardiovascular disease is the major cause of sudden death in patients with schizophrenia. The article was published in ***Schizophrenia Research*** and is one of the few of its kind presented pathological findings as a source of support.

In collaboration with colleagues from the Faculty of Medicine have managed to publish a comprehensive 15-year study on sudden death in the general population. The study results was published in ***American Journal of Forensic Medicine and Pathology***.

Among future directions for research include efficacy and safety of depot antipsychotics Generation II (second generation long-acting antipsychotics). The first step was taken by highlighting the efficacy of olanzapine long-acting in preventing relapse in schizophrenia with catatonic episodes and publishing the results in the ***American Journal of Therapeutics.***

Another topic for future research is to evaluate the efficacy and safety of clozapine administered to patients with mental retardation for aggressive behaviors.

Rezumat

Am absolvit Facultatea de Medicină Generală din cadrul Universității „Gr. T. Popa'' din Iași în anul 1999 după care mi-am început specializarea în psihiatrie din anul 2002 după concursul de rezidentiat. Am activat neintrerupt la Spitalul de Psihiatrie si Neurologie din Brasov inițial ca rezident din anul 2002 pană in 2007, continuând apoi ca specialist din 2007 pană in 2012. Am devenit medic primar psihiatru în anul 2012. Ca o recunoaștere a profesionalismului și a capacității mele organizatorice am fost numit Medic șef de secție din anul 2015. Sunt Președintele Comisiei de Etică in cadrul Spitalului și membru în Consiliul Medical.

În anul 2002 am devenit preparator universitar prin concurs la disciplina psihiatrie în cadrul Facultății de Medicină a Universității Transilvania din Brașov. Dezvoltarea carierei mele universitare s-a făcut prin parcurgerea tuturor etapelor promovate prin concurs: asistent universitar în 2009, șef de lucrari în 2012 și conferențiar în anul 2015.

În paralel cu activitatea clinică am desfasurat o intensă activitate de cercetare. Am inceput și finalizat la UMF „Gr. T. Popa'' Iași Teza de doctorat intitulată „Corelatii somato-psihice și evaluări terapeutice în clinica și tratamentul tulburarilor depresive''. Tema, de o reală noutate la vremea respectivă a abordat sindromul metabolic și implicațiile acetuia în tulburările afective.

După susținerea tezei de doctorat, am publicat peste 40 lucrări științifice în domeniile principale ale patologiei psihiatrice, 15 dintre acestea fiind publicate în reviste indexate ISI Thomson Reuters. Din totalul articolelor, 14 au fost publicate în calitate de prim autor. Publicațiile mele au cumulat un număr de 86 de citări și un indice H de 5 în baza de date Google Scholar și un indice H de 4 în baza de date ISI Thomson Reuters.

Mi-am inceput activitatea de cercetare științifică în studiile clinice in anul 2002, ca membru al echipei coordonate de doamna Prof. Univ. Dr. Victoria Burtea. Am participat astfel la cel mai important studiu european dedicat primului episod de schizofrenie (EUFEST) condus de Grupul European de Cercetare a Schizofreniei. Studiul a avut drept scop principal compararea eficacității și toleranței tratamentului cu antipsihotice atipice (amisulprid, quetiapină, olanzapină, zyprasidonă) față de haloperidol. Rezultatele acestui studiu rămân un reper și după 10 ani la fel ca replica sa americană, studiul CATIE.

Am participat în calitate de investigator în peste 20 de studii clinice care au dus la apariția pe piată a unor molecule importante pentru tratamentul afecțiunilor psihice majore (SeroquelXR, Zypadhera, Asenapina, etc) dar și la calibrarea pentru limba română a unor scale valoroase de evaluare clinică precum PETIT, RDQ, NSI-16, RISA, etc). Ca investigator

principal am participat la trialul clinic MIN-103 in cadrul programului EUDRA pentru precizarea eficacității și siguranței unei molecule noi destinate tratamentului schizofreniei.

Activitatea clinică intr-o secție de psihiatrie de urgență a condus la realizarea și publicarea a 2 studii extrem de importante asupra eficacității și siguranței titrării rapide a clozapinei în schizofrenie și tulburarea bipolara. Titrarea rapidă a clozapinei a trezit atenția unor nume mari în psihiatria mondială precum John M Kane, Christoph U Correll, Peter Manu care au acceptat să participe ca autori la publicarea articolelor in ***Acta Psychiatrica Scandinavica*** si ***Journal of Affective Disorders***. Studiile au reușit să demonstreze pentru prima dată la nivel mondial eficiența și siguranța administrării clozapinei prin metoda titrării rapide la pacienții cu tulburare bipolară I refractară la tratament.

Viața și problemele pacienților cu schizofrenie au fost printre prioritațile activității mele de cercetare. Incepând cu aspectele etice ale tratamentului cu antipsihotice depot de la primele episoade de psihoză și până la tratamentul femeilor cu schizofrenie care rămân sau doresc să ramână însarcinate. Astfel am publicat articole pe tema tratamentului antipsihotic în timpul sarcinii la pacientele cu schizofrenie precum și aspecte legate de internarea nevoluntara a acestor bolnavi. Rezultatele pot fi găsite în ***Therapeutics and Clinical Risk Management*** și în ***American Journal of Therapeutics.***

Instituționalizarea bolnavilor cu schizofrenie a fost și este o temă de interes pentru familie si societate prin multitudinea de aspecte pe care le implică: etice, morale, materiale, umane. Acest eveniment traumatizant pentru familie și pacient (instituționalizarea) generează costuri uriașe mai ales atunci cand varsta celor instituționalizati este în scădere așa cum se pare că se intampla în România. Am efectuat astfel un studiu publicat în ***Revista de cercetare și interventie socială*** care a demonstrat o tendință a societatii noastre de a instituționaliza acești bolnavi tot mai precoce.

Moartea subită a pacienților internați cu diagnosticul de schizofrenie a constituit o altă preocupare în activitatea de cercetare. Am dorit sa verific dacă tratamentul antipsihotic ar putea avea un impact in aceste cazuri. Studiul efectuat a aratat ca patologia cardiovasculară este cauza majoră a morții subite la pacienții cu schizofrenie. Articolul a fost publicat în revista ***Schizophrenia Research*** fiind unul dintre puținele de acest fel care a prezentat buletinele anatomo-patologice ca sursă de suport a concluziilor.

În colaborare cu colegii din Facultatea de Medicină am reușit să public un studiu amplu pe 15 ani asupra morții subite în populatia generală. Studiul efectuat a avut ca suport de documentare rapoartele de la Serviciul de Medicină Legală din Brasov. Bolile cardiovasculare nedepistate sau netratate constituie factorul major de risc pentru moartea

subită. Rezultatele au fost publicate în ***American Journal of Forensic Medicine and Pathology***.

Printre viitoarele direcții de cercetare științifică se numără eficacitatea și siguranța administrarii antipsihoticelor depot de generația a II-a (second generation long-acting antipsychotics). Primul pas a fost făcut prin evidențierea eficacitatii olanzapinei long-acting în prevenirea recăderii in schizofrenia cu episoade catatonice și publicarea rezultatelor in ***American Journal of Therapeutics.***

O alta temă de cercetare este evaluarea eficacității și siguranței clozapinei administrate la pacientii cu intărziere mentală internați pentru comportamente agresive.

SECTION B

SCIENTIFIC AND PROFESSIONAL ACHIEVEMENTS AND THE EVOLUTION AND DEVELOPMENT PLANS FOR CAREER DEVELOPMENT

(B-I) SCIENTIFIC AND PROFESSIONAL ACHIEVEMENTS

CHAPTER 1. MAIN RESEARCH AREA - DEVELOPMENT AND RESULTS: SCIENTIFIC ACHIEVEMENTS IN SCHIZOPHRENIA

1.1 The control of symptoms in acute psychotic episode

Ifteni P, Nielsen J, Burtea V, Correll CU, Kane JM, Manu P. Effectiveness and safety of rapid clozapine titration in schizophrenia Acta Psychiatr Scand. 2014 Jul;130(1):25-9.

One of the major concer about the treatment of schizophrenia is the control of agitation or aggressiveness caused by the psychotic symptoms. In many cases the level of psychopathology is so high that abrupt intervention is mandatory, epecialy for admitted patiets. In those cases clozapine could be ''the last resort''. Clozapine was synthesized in 1958 in Switzerland by researchers working with a group of tricyclic molecules similar to imipramine [1]. The new compound had neuroleptic properties and did not cause changes in muscle tone in animal experiments. Clinical studies performed by Hans Hippius starting in 1966 confirmed the antipsychotic effectiveness and the absence of severe or disabling extrapyramidal adverse reactions [2] Open labels trials continued in Europe until 1974 and the drug was approved for use in Europe in 1975 [3]. Unfortunately within 6 months of the introduction of the drug 17 cases of severe neutropenia or agranulocytosis was reported with eight fatalities among 3000 patients [4]. Following a landmark randomized trial [5] the Food and Drug Administration allowed its use in the United States in 1989 [6]. The drug is widely prescribed for the treatment of patients with schizophrenia refractory to other pharmacological interventions [7], a population in which the therapeutic benefits exceed the risk created by infrequent major adverse reactions (e.g., severe neutropenia and agranulocytosis, myocarditis, pancreatitis, venous thromboembolism and seizures) [8]. At the present time, although the administration of clozapine is considered the most effective pharmacological intervention for treatment-resistant schizophrenia in all national guidelines, its utilization is suboptimal due to physicians' concerns about tolerability and patients' inadequate adherence to hematological monitoring required for early detection of severe neutropenia [9]. Adverse drug effects lead to clozapine discontinuation in 17% of cases [10], a decision for which the patients' perspective may be just as important as the clinicians' assessment of the risk-benefit ratio of continuing the treatment [11]. Clinical guidelines and manufacturers' recommendations advise starting with 12.5–25 mg/day and gradual increase over a 2-week period until reaching the therapeutic dose. This recommendation has not been

derived from rigorous controlled trials, but rather from reports of severe hypotension observed during the initial clinical testing of the drug in the United States on prison inmates in 1974 (1) and case-series correlating high clozapine dosages with the occurrence of seizures (1, 12). The conservative "one size fits all" approach ignores the substantial differences in bioavailability observed after the administration of the same clozapine dose [13], a heterogeneity explained in part by the large number of genes that contribute to the metabolic performance of the cytochrome P450 system [14]. In addition, the slow upward titration delays control of psychotic symptoms, increases the need for additional "bridging" pharmacological interventions, and may unnecessarily prolong suffering and length of hospital stay.

The meaning of "rapid" clozapine titration is variable. A recent report has described "rapid" clozapine titration protocols used in Australia, according to which patients would be given a total of 612.5 mg or 812 mg in the first 9 days [15]. However, the drug was introduced by slow dose titration, usually starting with 12.5 mg on Day 1, 25 mg on Day 2, 50 mg on Day 3 and then up to the dose required to achieve safely the expected therapeutic effect. Within this framework, the odds-ratios for myocarditis were 1.24 (95% confidence interval 1.01–1.52) for each additional 250 mg of clozapine given in the first 9 days of upward titration.

Our idea was to treat patiets with clozapine in a much faster way. The patients described in this report were admitted to a 120-bed free-standing psychiatric teaching hospital located in Brasov, Romania. The clinical care is coordinated by board-certified psychiatrists affiliated with the local medical school. Patient population From January 1, 2009 through December 31, 2011 the hospital admitted 524 patients diagnosed with schizophrenia according to DSM–IV-TR criteria [16]. Within this cohort, 111 individuals (21.2%) required treatment with clozapine. Consent for treatment using this method was obtained in accordance with the procedures stipulated by the hospital's Ethics Committee. The rapid clozapine titration method was used on all patients who were treated with this drug, i.e., i) patients who had been previously discharged on clozapine, but failed to comply with treatment recommendations, and ii) patients whose agitation and "positive" symptoms could not be controlled with other neuroleptics.

Oral administration of clozapine was started with a dose of 25 mg, followed by additional doses of 25–50 mg administered as needed every 6 h in the first 24 h. Dose adjustments taking into consideration the response to treatment were allowed. On subsequent days the dose was increased by not more than 100 mg each day until satisfactory symptom control, i.e. absence of behavior dangerous to self or others and remission or substantial reduction of

positive symptoms. The clozapine dose was kept stable or decreased according to clinical assessment of symptom control. Moodstabilizers or benzodiazepines were avoided during the titration period. Clinical and laboratory assessments Blood pressure, heart rate and temperature were recorded daily. A complete blood count, metabolic panel and an electrocardiogram were obtained on admission. Complete blood counts were checked weekly throughout the hospital stay. The severity of illness was assessed with the Positive and Negative Syndrome Scale (PANSS) [17] and Clinical Global Impression Scale (CGI) [18] at the time of admission and on the day of discharge from the inpatient service. Adverse drug effects were assessed daily throughout the hospital stay.

Demographic, clinical and clozapine-related characteristics of patients previously exposed to the drug and those of patients who had received clozapine for the first time after failing to respond to other antipsychotics during the hospital stay were compared using analysis of variance.

Clozapine was administered according to the rapid titration method to 111 patients (age 41.1 ± 11.2 years, 52.3% males). The mean age at onset of schizophrenia was 23.7±7.0 years and the duration of illness at the time of the admission was 18.6 ± 9.5 years. Assessments of the severity of illness indicated a mean PANSS score of 104.1± 3.8 and a CGI score of 5.6 ± 0.6. The global assessment of function (GAF) had a mean score of 21.4 ± 6.8, indicating significant impairment (Table 1).

Table 1. Demographic and psychiatric characteristics on admission

Characteristic	Total (N = 111)	Prior exposure to clozapine (N = 73)	No prior exposure to clozapine (N = 38)	P
Age, years ± SD	42.1 ± 11.3	42.6 ± 11.2	41.2 ± 11.6	0.536
Male Gender, N (%)	58 (52.2%)	39 (53.4%)	19 (50.0%)	0.731
Smoking, N (%)	99 (89.18%)	68 (93.15%)	31 (81.57%)	0.032
Schizophrenia type				
Paranoid	72 (64.9%)	52 (71.2%)	20 (52.6%)	0.073
Undifferentiated	20 (18.0%)	9 (12.3%)	11 (28.9%)	
Disorganized	19 (17.12%)	12 (16.44%)	7 (18.4%)	
Age of onset, years ± SD	23.5 ± 7.0	23.5 ± 7.4	23.5 ± 6.3	0.97
Duration of Illness, years ± SD	18.56 ± 9.5	19.1 ± 9.4	17.7 ± 9.7	0.461
GAF, score ± SD	21.4 ± 6.8	20.8 ± 6.9	22.4 ± 6.4	0.254
CGI, score ± SD	5.6 ± 0.6	5.7 ± 0.5	5.6 ± 0.6	0.481
PANSS, score ± SD	104.1 ± 3.8	104.3 ± 2.9	103.8 ± 5.1	0.483

GAF, global assessment of function; CGI, clinical global impression; PANSS, positive and negative symptom scale.

The average clozapine dose during the first 24 h was 129 ± 75 mg (range 25–400 mg). Satisfactory symptom control was obtained on average with 371.9 ±181.2 mg/day after 5.1 ± 4.0 days. After a hospital stay of 28.3 ± 13.6 days, the PANSS score at discharge was 60.3 ± 6.1 (Table 2). None of the patients experienced seizures, syncope or symptomatic hypotension, agranulocytosis or other major complications.

Seventy-three of the 111 patients (mean age 42.6 ± 11.2 years, range 24–64 years had previously been treated with clozapine for an average of 31.5 months with an average dose of 296 mg/day.

These patients had stopped taking clozapine on their own and the time interval from the last dose to the onset of relapse could not be assessed. This group was treated with clozapine as soon as they were admitted. Thirty-eight patients (mean age 41.2 ± 11.6 years, range 26–69 years) were treated with clozapine after failing to respond to other antipsychotics.

Table 2. Clozapine dosage and duration of hospitalization

Characteristic	Total (N = 111)	Prior exposure to clozapine (N = 73)	No prior exposure to clozapine (N = 38)	P
Dose on first day of treatment, mg ± SD	129.1 ± 75.4	115.1 ± 52.7	155.9 ± 101.9	0.006
Maximum dose, mg ± SD	371.9 ± 181.2	352.7 ± 176.1	408.6 ± 187.5	0.124
Duration of hospitalization, days ± SD	28.3 ± 13.6	25.3 ± 12.3	33.9 ± 14.4	0.001
PANSS at discharge, score ± SD	60.3 ± 6.1	60.5 ± 5.4	59.8 ± 7.4	0.539
Day of Maximum dose, days ± SD	5.1 ± 4.0	4.2 ± 3.1	7.1 ± 4.9	0.001
Dose at discharge (mg/day)	351.6 ± 140.5	333.6 ± 134.6	368.4 ± 149.9	0.06

PANSS, positive and negative symptom scale.

The clozapine dosages were increased faster in this switch group, as they had been severely ill in the hospital longer than patients off antipsychotics who were started onclozapine on admission. The clozapine dose used in the first 24 h was significantly lower (115.1 vs. 155.9 mg, P = 0.006) and the time required for satisfactory symptom control significantly longer (4.2 vs. 7.1 days) in the group of patients with prior exposure to the drug. The dose ranges in the first day of treatment were 25–300 mg in the group with prior exposure to clozapine and 25–400 mg in the remaining patients.

No major adverse drug effects were reported to the inpatient team by the affiliated outpatient psychiatric providers during the first month after discharge.

We reported that rapid titration dosing regimen of clozapine appeared safe in both clozapine na€ıve patients and previous users of clozapine. In our sample, patients reached on average 129 mg during the first 24 h of treatment, which by traditional dosing regimen is not reached until 4–6 days of treatment. The findings must be interpreted with caution, given the limitation of a study with 111 subjects and the absence of a randomized control group treated with the traditional slow upward titration of clozapine. In addition, plasma levels of clozapine and norclozapine were not measured. The cohort design was used because this is the first study to abandon the conventional approach and the primary aim was to assess the safety and

feasibility of a rapid dosing regimen. Rapid titration was safe, as none of the lifethreatening adverse effects of this drug were observed. Such complications are quite rare; the incidence of agranulocytosis is 0.4–0.8%, that of myocarditis is 0.007% [19]. The results of an Australian study indicating a relationship between a faster upward titration and the incidence of clozapine-induced myocarditis have not been confirmed and stand in contrast with the understanding that the myocardial fraying and eospinophilic infiltrate observed in this condition do not represent a direct cardiotoxic effect, but arerather similar to a hypersensitivity reaction. Myocarditis is not considered to be a dose-dependent condition, as its onset has been observed at dosages in the range 100–450 mg/day in Australia [20] and 50–750 mg/day elsewhere [21]. None of the patients had seizures, symptomatic orthostatic hypotension, clinical evidence (concomitant rigidity and fever) suggestive of neuroleptic malignant syndrome, new onset of glucose intolerance, or evidence of significant gastrointestinal hypomobility. Again, however, the size of our study population and the low probability of life-threatening complications such as drug-induced myocarditis and agranulocytosis may explain the complete safety in the setting in which it has been tried, but may become subject to change as our technique is tested in larger patient samples. Therefore, we recommend daily and close monitoring of physical condition during rapid titration, with particular attention to flu-like symptoms, dyspnea, palpitations, chest pain, new onset edema and easy access to echocardiography to detect sytolidc dysfunction, hypokynesia and/or pericardial effusions. One of the advantages of a rapid titration regimen may be that benzodiazepines can be avoided as these combinations have previously been associated with increased risk of sudden death [22]. In our study concomitant administration of mood stabilizers and benzodiazepines were avoided because of safety reasons and satisfactory symptom control was achieved after only 5 days. In addition a dramatic reduction in PANSS total score was seen at discharge, despite a total PANSS score of 104 at admission. A possible drawback of a rapid dosing regimen is that patients may end up receiving higher dosages than necessary, but this is less likely to have occurred in this study because the maximum and end dose is comparable to other studies not using a rapid titration regimen. Nonetheless, while our utilized protocol might increase the risk of excessive sedation and orthostatic hypotension, this was avoided in our study by dosing every 6 h during the first 24 h in order to establish the tolerability of clozapine at an individual level. With this approach, none of the patients developed serious side effects during the study. Therefore, we were not able to identify any subgroup of patients where rapid dose titration not should be applied. However, the study population was rather young (mean age of 41 years), and rapid titration

of clozapine may be less tolerated in older patients taking other medications that may lead to orthostatic hypotension, such as diuretics and betaadrenergic blockers, and patients with poor oral fluid intake.

In conclusion, this study suggests that the traditional dosing regimen may be abandoned in patients where rapid symptom control is warranted. Our findings should lead to the conduct of large scale, double blinded, randomized studies [23]. Future studies should also explore the data contained in national clozapine registries in order to detect any rare, but serious, adverse drug reactions in patients undergoing rapid titration [24].

1.2 Therapeutic measures in involuntarily admitted patients

Ifteni P, Szalontay AS, Teodorescu A.Reducing Restraint With Clozapine in Involuntarily Admitted Patients With Schizophrenia. Am J Ther. 2016 Nov 24. doi: 10.1097/MJT. 0000000000000533

In settings for acute psychiatric patiets dealing with ,,challenging behaviour,, is one of the most common and dificult situation. In the entire world, restraint and seclusion are common interventions in psychiatric in-patient settings due to aggressive behavior [25]. Since the 1990s there is a growing interest in the incidence of coercive measures in most European countries [26]. During the last years, there have been a few European studies, in which psychiatric hospitals were compared regarding the frequency and duration of coercive measures. These studies are from the UK [27], Switzerland [28], Finland [29] and Germany [30]. To date, there is no available data for Romania regarding this topic. Because of possible physical and psychological damage on patients affected by coercive measures [31], the use of coercive measures can be seen as an indicator of the quality of psychiatric inpatient treatment.

In this study, we assessed antipsychotic use in involuntarily admitted patients with schizophrenia to (1) test the anti-aggressive properties of clozapine by recording time until first use of restraint past admission and (2) to identify risk profiles for early restraint use in this population. Data were collected from charts, covering the period 2011-2014 during routine clinical care in the Psychiatry and Neurology Hospital, Brasov, Romania. This hospital is a public care facility which covers a population of 400000. The admission ward is a 120 bed facility with 24 h service of board certified psychiatrists. Data from all subjects with schizophrenia (clinical DSM-IV-TR diagnosis), who were admitted involuntarily with the diagnosis of schizophrenia were extracted. Due to our earlier report on fast titration of clozapine [32] our hospital policy permitted the early use of clozapine as an equal alternative to other first generation (FGA) and second-generation antipsychotics (SGA). Antipsychotic choice during the early admission was however the sole responsibility of the respective psychiatrist on duty in the emergency room/ the admission wards. Restraint order was written whenever subjects appeared to be a threat for staff or fellow patients. Due to clinical departmental policy Positive and Negative Symptoms Scale (PANSS)[33] and Clinical Global Impression (CGI) [34] were recorded during admission in all subjects. This study was approved by the local ethics committee and with the Helsinki Declaration of 1975/2000.

We divided the patients in two groups. The clozapine group (CLZ-group) included all cases treated with clozapine during admission. In the non-clozapine group (non-CLZ) we entered all patients treated with another antipsychotics (haloperidol, olanzapine, quetiapine, risperidone, amisulprid and aripiprazole). The primary aim of the study was to identify the index incident of restraint and the duration until restraint past admission. Demographic data included gender, age, duration of illness, and age of onset. We also collected data regarding reason for admission, number of restraints, length of stay, previous involuntary admissions, and history of violence.

We collected data from 115 consecutive patients with schizophrenia (51.3% male, 39.6 ± 11.05 years; mean/SD), who were admitted involuntarily to Psychiatry and Neurology Hospital, Brasov, Romania during 01.01.2011 – and 31.12.2014. Based on clinical decisions of their treating psychiatrists, subjects were started onthe following antipsychotics: haloperidol (n=81; 70.4%), clozapine (n=13; 11.3%), olanzapine (n=12; 10.4%) or other SGAs (7.9%; including amisulpiride: n=3, quetiapine: n=3, aripiprazole: n=2, risperidone: n=1).

To test the immediate effect of early clozapine use restraint characteristics were contrasted for subjects receiving clozapine as the first antipsychotic during this hospitalization. Moreover, these analysis were repeated for the CLZ group as well as for non-CLZ group. Accordingly, clinical and demographic characteristics were analyzed and compared for these respective subgroups. In addition to the 13 subjects, who received clozapine as the first antipsychotic immediately after hospitalization (and receipt of white blood count), 11 subjects received clozapine as the 2nd intention. The median duration until clozapine was started as a 2nd option was 11.1 ± 4.1 days. The median duration of clozapine treatment was 19.5 (11.2; 23) days; clozapine was up-titrated during 5 ± 2.2 days, to a mean maximal dose of 437.5 ± 132.1 mg.

Due to the naturalistic nature of the study, demographic, clinical and treatment characteristics of subgroups differed slightly (Table 1). In particular, the subgroup of subjects, in whom clozapine was used as the first antipsychotic (CLZ-1st) included a significantly higher proportion of subjects, who were admitted involuntarily due to self-destructive behavior (53.8%) compared to the remaining cohort (21.5%; p=0.002), while the externally targeted violence was the main reason for involuntary admission in the remaining cohort (see Table 1). Moreover, the clozapine group included more subjects with a longer hospitalization-free period prior the current admission (median period past prior hospitalization 220 days vs. 90 days; p=0.005). Nevertheless, all other clinical and demographic parameters, in particular

those characterizing disease severity and aggressive potential did not differ between antipsychotic treatment groups (see Table 1).

	Total (n=115)	**Clozapine** n=24 (19.30%)	**Subgroup: Clozapine 1st AP** n=13 (11.3%)	**Non-CLZ** n=91	**p-value CLZ vs. Non CLZ**	**p-value CLZ 1st vs. Others**
Age (years; mean, SD)	39.67 ± 11.05	36.92 ± 8.42	37.15 ± 8.59	40.40 ± 11.57	0.17	0.37
Sex, male (n,%)	59 (51.30)	15 (62.5)	10 (76.92)	44 (48.3)	0.25	0.08
Age at Onset (median; 25st; 75st percentile)	25.0 (22.0; 30.0)	18.25 (22.5;24.75)	23 (21; 24.5)	26 (22; 33)	**0.002**	0.07
Illness Duration (yrs; median; 25st; 75st percentile)	12 (3;20)	11 (6;22)	11 (9;16)	9 (3;20)	0.22	0.30
Reason for Involuntary Admission: Threat for /Violence against others/objects (n,%) Threat for /Violence against self (n,%)	86 (74.78) 29 (25.22)	14 (58.33) 10 (41.67)	6 (46.15) 7 (53.85)	72 (79.12) 19 (20.88)	0.06	**0.02**
MOAS total (mean, SD)	11.25 ± 1.67	11.23 ± 1.56	11.61 ± 1.66	11.23 ± 1.70	0.92	0.46
MOAS Verbal Aggression (mean, SD)	3.19 ± 0.67	3.41 ± 0.65	3.38 ± 0.65	3.13 ± 0.70	0.06	0.27
MOAS Aggression against Property	2.53 ± 0.98	2.60 ± 0.97	2.69 ± 0.27	2.51 ± 1.00	0.50	0.54
MOAS Physical Aggression	3.04 ± 0.67	2.80 ± 1.02	2.92 ± 0.28	3.07 ± 1.01	0.18	0.76
MOAS Autoaggression	2.49 ± 0.87	2.50 ± 0.93	2.61 ± 0.77	2.8 ± 0.65	0.90	0.53
PANSS at Admission (median; 25st; 75st percentile)	100 (98;104)	102.7 (99; 106.5)	101 (98.5; 106)	100 (98; 104)	0.43	0.58

	Total (n=115)	**Clozapine** n=24 (19.30%)	**Subgroup: Clozapine 1st AP** n=13 (11.3%)	**Non-CLZ** n=91	**p-value CLZ vs. Non CLZ**	**p-value CLZ 1st vs. Others**
PANSS hostility	5 (5; 6)	6 (5; 6)	6 (5; 6.5)	5 (5;6)	0.14	0.28
CGI at Admission (median; 25st; 75st percentile; range)	6 (6; 6; 5-7)	6 (6; 6; 5-7)	6 (6; 6; 6-7)	6 (6; 6; 5-7)	0.47	0.40
History of Violence (n,%)[a)]	66 (57.90)	21 (91.30)	10 (83.33)	45 (49.45)	**0.0003**	**0.07**
History of Involuntary Admission (n,%)	21 (18.26)	11 (45.83)	7 (53.85)	10 (10.99)	**0.0003**	**0.002**
Number of Previous Hospitalizations within prior 12 months; median (25th; 75thpercentile; range)	1 (0; 1; 0-5)	1 (0; 1; 0-3)	0 (0;1; 0-3)	1 (0; 2; 0-5)	0.94	0.31
Days since prior Hospitalization (median; 25st; 75st percentile)[b)]	120 (60; 240)	210 (121; 300)	220 (104.75; 300)	90 (45; 217)	**0.005**	0.14
Length of Stay	27.33 ± 9.14	26.3 ± 9.77	24.23 ± 9.61	27.5 ± 9.02	0.46	0.06

Restraint was used in the vast majority (n= 103; 89.5%) of the cohort anytime during the hospitalization. Mostly, restraint was used very early during the admission (Median time until restraint: 3 hours; 25th/ 75th percentile: 0.25; 48 h). These parameters were strikingly lowered in the CLZ-1stgroup; in which only three subjects (23%) experienced restraint (p>0.0001 relative to the remaining cohort), with a median time until restraint of 408 hours (25th/ 75th percentile: 48; 540; p>0.0001; table 2). In the non CLZ group the proportion of restraint was significantly higher (n=87, 95.6%). Similarly, restraint reduction and delay of restraint was observed for the clozapine group. (see Table 2). Moreover, the rate of restraint was 23% for clozapine compared with 95% for haloperidol and 100% for another SGAs (risperidone, olanzapine, amisulprid, aripiprazole and quetiapine.

As a minimal preparation time to obtain a baseline white blood count of at least one hour appears mandatory, we performed a secondary survival analysis for the first week of hospitalization for all subjects, who had not needed restraint within the first hour past admission This analysis involved 69 (60%) of the initial 115 subject and included the CLZ-1st subgroup in total (18.8% of this 1h-restraint free group) as well as the 56 (81.1%) Non-CLZ subjects, who were restraint-free past one hour. A significant group separation was noticeable during the first 24 hours and persisted throughout the observation period (Log-rank X^2 = 9.96; p=0.0018).

Table 2: Use of Restraint in Involuntarily Admitted Subjects with Schizophrenia.

	Total (n=115)	**Clozapine** (n=24)	**Subgroup: Clozapine 1st AP** (n=13)	**Non-CLZ** (n=91)	**p-value CLZ vs. Non CLZ**	**p-value CLZ 1st vs. Others**
Restraint anytime during hospitalization; n (%)	103 (89.5)	16 (66.6)	3 (23.0)	87 (95.6)	0.0003	<0.0001
Hours until Restraint[b]; median (25th; 75thpercentile; range)	3 (0.25; 48)	118 (24; 426)	408 (48; 540)	1.1 (0.2; 24)	<0.0001	<0.0001
Restraint during 1st 24h; n (%)	71 (61.7)	5 (20.8)	1 (7.6)	66 (72.5)	<0.0001	<0.0001

[b]for subjects without any restraint, the length of stay is substituted as restraint-free period.

To exclude the possibility that the delay of restraint was primarily mediated by clinical factors but treatment characteristics, we used stepwise forward regression including subgroup CLZ-1st, age, gender and reason for admission as potentially predictive factors. Of these, only CLZ-1st and the reason for admission entered the final significant model and CLZ-1st was the sole significant factor within the model.

Within the limiting framework of a retrospective observation of naturalistic treatment, this study suggests the possibility that the anti-aggressive properties of clozapine can be clinically efficiently used in a highly problematic cohort of involuntarily admitted subjects with schizophrenia.

Therapeutic strategies to reduce violence in patients with schizophrenia suffer from a lack of guiding information from randomized studies and prospective studies are methodologically highly limited due to an inherent selection bias related to informed consent in a predominantly un-cooperative study group [35]. Thus, our naturalistic small cohort is thought

to contribute to existing clinical expertise despite the limitation of a non-randomized retrospective study design.

Coercive treatment includes both, physical restraints and involuntary medication, however rarely can involuntary medication be replaced by physical restraint, while the reverse is realistically achievable. Both of these measures are unfortunately frequent during involuntary admissions [35]. Due to the high medical risks including death associated with restrain [37] and due to the traumatic experience associated with restraint, these numbers sorely need to decrease.

Based on our earlier observation of fast clozapine titration, our hospital policies permitted the use of clozapine as an emergency medication without written consent from the patient; we were thus in the exceptional position to make use of the well-established anti-aggressive properties of clozapine [38] during early hospitalization. Our data showed a striking reduction of restraint rates with clozapine use, relative to the predominantly haloperidol treated remaining subjects. Importantly, despite the naturalistic study design, clinical and demographic factors did not significantly influence the restraint-free period, the use of clozapine as the first antipsychotic was the sole characteristic significantly associated with delayed restraint. These results are in line with earlier studies on the effects of clozapine on restraint frequencies chronic schizophrenia [39,40], but our results are novel in that clozapine was used as first-line medication. Dispate limitations, the clinical meaningful of the findings are very important for psychiatrists. Further studies are necessary to validate our results.

These retrospective data suggest an early anti-aggressive effect of clozapine during the immediate use of clozapine in highly problematic patients. Further randomized and controlled studies are necessary to validate our results. Reducing stress and stigma of patients with schizophrenia must be the core objective of professionals in this field alongside with achieving remission.

1.3 The management of relapse prevention in schizophrenia

1.3.1 Predictors of relapse in schizophrenia

Schizophrenia is a chronic disease, and the problem of non or partial compliance represents a major challenge to successful treatment outcomes. The value of long-term antipsychotic drug treatment in reducing the frequency of relapses and admisions has been clearly demonstrated in a number of long-term trials. A review of 6 studies showed a mean one year relapse rate of 74% placebo treated patients versus 16% of patients who were correct medicated during this period [41,42]. Among patients experiencing relapse, episodes are less severe in those who adhered to a medication compliant. Compliant patients are less likely to have episodes characterized by self destructive behaviour, violent behaviour and antisocial acts [43]. Non adherence to prescribed regimen may impact negatively an prognosis, especially in patients who are in the early stages of schizophrenia [44, 45]. It can also compromise a patient's daily functioning and quality of life [46]. The risk for non-compliance and partial compliance are exacerbated by the autonomy of the outpatient setting [47]. The most tragic result of treatment failure, for both patients and their families, is suicide. Risk for suicide is increased in schizophrenia and is highest in men. A meta analysis of 29 studies found a significant increase in suicide in patients who were noncompliant or partially compliant with treatment [48]. Recent literature reported that only about one-third of patients with schizophrenia are to be fully compliant, another third are said to be partially compliant, meaning that these patients will either reduce the dose of the drug prescribed or fail to take medication from time to time. The remaining patients do not follow prescription instructions at all [49-51].

The factors influencing compliance related to the patient's environment (negative attitude toward psychiatric treatment of patient family and the media, poor social rapport when the patient is living alone, "low" social rank of illness, and attitude toward the illness and its treatment in the social and therapeutic environment were also investigated [52].

In our study we examined all the male and female patients diagnosed with schizophrenia (DSM-IV), who were experiencing an acute relapse that required hospitalization between 1 January 2008 and 31 Decemeber 2009. The setting was the Psychiatry and Neurology Hospital Brasov. We collected demographic data, the type of hospitalization (presenting in emergency, sending by GP, specialist or inter-hospitals transfers, criteria of hospitalisation (emergency, hospitalized for diagnosis, for treatment, etc), the modality to present: alone, with family or friends, with ambulance and police and treatment compliance declared by the patient or informants.

Between 1 January 2008 and 31 December 2009 there were hospitalized 986 patients with

schizophrenia 485 in 2008 and 501 in 2009, 53,85% female and 46,15% male in both years, F/M = 1,16 , 13,43% aged under 30 years, and 86, 57% between 31 and 65 years. Any way 54.16% were between 31-50 years; 76,67% patients from urban area, 23,33 from rural area, 57,90% unmarried, 25,05% married, 17,04% divorced.

One of the most important finding of our study was the fact that the majority of hospitalisations of patients with schizophrenia were voluntary 98,69%.

Data suggested that 63,18% of those voluntary hospitalised patient were fully or partially treatment compliant (self report). Only 35,97% self declared full noncompliant comparative with 100% nontreatment compliant in the case of involuntary hospitalisation.

An interesting finding in our study according to the type of hospitalisations of patient with schizophrenia was the fact that the greatest part of those patient (89,53%) addressed for hospitalisation alone, brought by family members or sent by GP. Only 1,92% were brought by police and ambulance and 1,66% were hospitalisations through inter-hospital transfer.

The greatest full self declared treatment compliance belong to the patients with schizophrenia coming alone or with family. Another important aspect resulting from the study was the reduced number of patients with only one hospitalisation in the period of time under the study (81,4%) and only 5,28% patients with schizophrenia were hospitalised more than 3 times in that period.

Every-day clinical practice conditions studied retrospectively over a long period of time (two years) about the type of hospitalization of patients with schizophrenia evidenced the fact that the greatest part of 77.58% those patients presented at emergency room came alone or accompanied by the family. Consecvently, the greatest part of all the patients with schizophrenia hospitalized in that period of time agreed with the hospital setting, only a minority 1,3% of them were unvoluntary hospitalized.

An other finding of the study was the fact that between the patients with schizophrenia voluntary hospitalized 52,43% were full treatment compliant, 10,75% were partial treatment compliant and 35,97% were noncompliant with antipsychotic medication, according with self rapport.

Women seem to be more likely to comply with antipsychotic medication than men 75,70% in outpatient setting, comparative with 25,30% male; also women were totaly uncompliant 14.70%, comparative with 62.80% man in our study. Those findings are similar with data from other study [53].

All the patients compulsory hospitalized were 100% treatment noncompliant in our study.

Studing the number of hospitalization every year we had notice that patients with

schizophrenia self treatment compliant had only 1 hospitalization per year, instead of the other that had 2-5 hospitalization per year. Thus, the inadequacy of schizophrenia treatment has high costs for both patients and society as a whole. The economic burden to society is generated largely by relapse and rehospitalisation, as the other noticed [54].

Comorbid substance abuse has been shown to have a negative influence on compliance in patients with schizophrenia [55, 56]. In our study 5,68% from all the hospitalized patients in that period of time had this comorbidity.

Despite the fact improve compliance in patients suffering from schizophrenia remain an important issues, compliance rates have remained basically unchanged. Therefore, following Heisenberg's principle, it must be assumed that any clinical research carried out to investigate compliance will have an influence on compliance itself and perhaps this is the most important finding of our study.

1.3.2 The management of relapse prevention in schizophrenia

Ifteni PI, Teodorescu A. Prevention of Catatonia With Olanzapine Long-Acting Injectable. Am J Ther. 2016 Aug 17

Schizophrenia is a chronic and disabling illness, with the majority of patients experiencing multiple relapses during the course of the illness. Relapse, characterised by acute psychotic exacerbation or catatonia may have serious implications such as high risk of patients harming themselves or others, aggresiveness, poorer educational staus and stigmatisation. Catatonia is a potentially life-threatening but treatable neuropsychiatric syndrome which has been associated with schizophrenia, but which may occur also in other psychiatric, metabolic, or neurologic conditions. The symptoms include rigidity, negativism, mutism and waxy flexibility.

The most important differential diagnosis of catatonia is neuroleptic malignant syndrome phenomenon known as catatonic dilemma [57, 58]. The literature doesn't disclose cases of catatonic prevention after starting LAIs (long acting injectables) and, as far as we know, there are no papers published regarding this topic.

LAIs were developed after the second half of last century in the attempt to improve adherence in schizophrenia, but challenges of long-term treatment outcomes still remain [59].

The pamoate salt of olanzapine is one of the second-generation antipsychotic depot formulations whose efficacy and safety in the treatment of schizophrenia has been previously documented [60,61].

The common recommendation is to avoid antipsychotics, at least during the early phases of catatonia treatment, to avoid antipsychotic-associated neuroleptic malignant syndrome (NMS), which has been believed to occur in up to 10 % of the catatonic patients treated with antipsychotics [62,63].

We present the case of a young woman with prior catatonic relapses before starting the treatment with second generation LAI (olanzapine pamoate). Informed consents for publication have been obtained from patients and are available for the editor.

The patient was a 31 year old divorced Caucasian female living with her parents in an urban area. She was diagnosed with paranoid schizophrenia at the age of 22, before Graduation of the Faculty of Economics. After the first admission in the Psychiatry and Neurology Hospital of Brasov, Romania she managed to complete her studies but soon relapsed with the second paranoid episode. As a particularity of the case we noted the evolution with 3 paranoid

episodes followed by the last 3 consecutive catatonic episodes between 2009 and 2011. The patient's files and her family statements revealed that the side effects were the main reasons for the patient's non-adherence to the antipsychotic treatment: haloperidol induced acute dystonia, risperidone induced akatisia and amisulprid induced amenorrhea. The patient response was very good to olanzapine 10 mg/day, but the patient followed the treatment only for a short period of time (2-3 months) after discharge. The paranoid episodes consisted in auditory hallucinations, persecutory delusions and aggressive behavior. Usually, she was admitted in the Acute Psychiatric Department involuntarily. After 4 years she was medically retired and she spent all day smoking and watching TV with minimal social interaction.

In August 2011 she suddenly became bizarre with refusal of meals and leaving her bed. After 2 days of mutism and total refusal of any food or water, she was admitted into an emergency psychiatric unit. The patient's brother affirmed that he was pretty sure that a new catatonic episode occurred (similarity with the previous two catatonic episodes was striking) and he decided to ask for psychiatric help immediately. He also declared that 4 months ago, at the end of April 2011, the patient informed her family using the sentence: "I'm cured and the treatment is no longer needed". Despite her family and the psychiatrist warnings she refused to follow the antipsychotic treatment with oral olanzapine. During the medical examination she showed passive resistance to any attempts to move her arms and legs with waxy flexibility. Routine complete blood count (CBC), electrolytes, creatinine, and liver function tests were normal as well as the ECG. Urine toxicology was negative. The patient had normal vital signs. The brain CT scan with contrast substance was normal.

According to the clinical features, laboratory results, CT scan images and absence of the antipsychotic treatment for more than 4 months we excluded NMS and the diagnosis was catatonic schizophrenia.

She was given oral lorazepam 3 mg/day (in absence of intramuscular or intravenous formulations of lorazepam at site) and glucose 5% 1000 ml/day for hydration and olanzapine 10 mg/day intramuscular from the second day.

The patient was responsive and after 3 days she started to eat and drink. The treatment continued with oral olanzapine 10 mg/day and than 20 mg/day leading to improvement of her condition. After two weeks she was given olanzapine long-acting injection 300 mg/intramuscular with no sign of PIS (post injection syndrome). She was discharged in highly improved condition after 4 weeks, with the recommendation of continuing treatment with olanzapine pamoate 300 mg/i.m. at every 2 weeks.

After the last hospitalization she had monthly appointments to a psychiatrist and continued the treatment with olanzapine pamoate 300 mg twice/month for 3 years. In this period she was in remission, she was part-time employed to a pizza house, and established a relationship. Her life became quite normal and her family was satisfied and affirmed that they fully trust the efficacy of this treatment.

Since May 2014 she continued the treatment with olanzapine pamoate 300 mg once/month at the recommendation of her psychiatrist. A subsequent follow up, after starting LAI, found her in remission with good and no relapses, incomparable with the time before LAI.

Catatonia is a syndrome caused by a variety of brain diseases and continues to be a potentially lethal condition. We present a case of young woman with schizophrenia and prior relapses who started olanzapine long-acting injection after her 3rd consecutive catatonic episode. She has been in full remission for almost 5 years under treatment with olanzapine LAI which provide long-term efficacy and safety of this formulation.

Standard care of catatonia includes hydration, nutrition, cooling, prevention of aspiration and thrombophlebitis. Benzodiazepines, especially lorazepam intravenously (2-5 mg), are widely recommended as a first choice of drugs for the treatment of catatonia [64, 65]. When benzodiazepine therapy fails, or the patient's condition is severe, electroconvulsive therapy is the treatment of choice for this disorder [66].

Despite the fact that the role of antipsychotics in treatment of catatonia is still controversial, we successfully treated patients after exclusion of the NMS diagnosis.

We strongly remind that catatonia can occur in patients with schizophrenia anytime after they discontinue antipsychotic treatment even in the absence of previous catatonic episodes.

1.4 Institutionalization in schizophrenia

Szalontay, A., Pascu, A.M., Teodorescu, A., Minea, D., Ifteni, P. Actual Tendency in Institutionalization of Patients with Schizophrenia. Revista de Cercetare si Interventie Sociala.2015. 51, 64-71.

At the beginning of the 20th century long stay institutional treatment was the norm for people with schizophrenia in absence of antipsychotic drugs. Hospitals with many beds were established in isolated forest or in rural areas where patients remained for extended periods of time. This situation has led to mental illness stigma amplification, particularly for schizophrenia. There were a lot of pictures in magazines and journals with disheveled and strange looking people, often assuming unusual poses or grimacing and gesturing in incomprehensible ways. There were a lot of scary stories about this patients and treatment used by physicians trying to cure them. As a result of these, society tried to isolate those patients and only in a few cases they manage to be accepted in local community.

When chlorpromazine was introduced for the treatment of people with schizophrenia in the middle of 50's, reduction of psychotic and disorganized symptoms had an enormous and significant impact on lengthy hospital stays for schizophrenic patients. As a consequence the number of beds for chronic patients was reduced in the majority of western countries by the late 1970s. Long-stay care was maintained only for those who were non-responsive to the effects of antipsychotic treatments. The treatment model for schizophrenia has changed during past decades, in terms of antipsychotics types and admission that averaged 6–12 weeks for acute patients 25 years ago, to up to 21 days in Romania or even 5–7 day stays in some countries like United States.

In Brasov County, despite the development of private psychiatric sector there is a tendency to institutionalize patients with schizophrenia at young age. The factors involved in this situation could be economic status, short time allocated by parents, lack of support from institution and local authorities, low level of education, and treatment resistance.

In contrast to non-institutionalized patients, they had substantial positive and negative symptoms [67], had cognitive impairments [68], significant functional impairments [69], and substantial levels of aggressive and unpredictable behaviors [70].

The study was conducted in Psychiatry and Neurology Brasov Romania in 2015. The patients described in this report were admitted to a 120-bed, free-standing psychiatric teaching hospital located in Brasov, Romania. Patients referred for hospitalization are admitted, on

alternate days, to one of the two units. The clinical care is coordinated by board-certified psychiatrists affiliated with the local medical school. There were collected data of 322 patients with schizophrenia institutionalized in Hospital for Chronic patients Vulcan, Brasov. The time period was between 1995 and 2015. The data included demographics, age of onset, duration of illness, treatment, education, marital status and economic status and the age of institutionalization. From patient's files we obtained information regarding relapses in previous 2 years before institutionalization, time from discharge to the next admission, the length of stay and the reason for family request for this hospitalization.

We divided patients in two groups: A, admitted between 1995 and 2004 and B admitted between 2005 and 2014. The aims were to verify if the age of the patients admitted for long stay in a chronic setting is higher in group A compared with Group B. The hypothesis was that age of patients admitted in present days is lower than 15-20 years ago.

Of 322 patients 189 were female (58.7%) with the mean age of 54.31years (SD=9.32) and 133 male (41.30%) with mean age 52.60 years (SD=11.22). In group A of patients admitted between 1995 and 2004 were 150 cases, with mean age 57.08 years (SD=5.67), age of onset 21.73 years (SD=3.34), and age of institutionalization 49.34 years (SD=8.86). In group B of patients admitted between 2005 and 2014 were 172 cases, mean age 51.15 (SD=9.15), age of onset 23.56 years (SD=4.11), and mean age of institutionalization 42.22 years (SD=7.76). The number of patients with age below 40 years was 12 (8%) in group A and 28 in group B (16.2%). In the table 1 are presented the demographic data of institutionalized patients.

Table 1. Demographics

Variables	All patients N=322	Institutionalized patients				*p*
		Group A 1995-2004 (N=150)		Group B 2005-2014 (N=177)		
		N	%	N	%	
Age (mean, SD)	53.45 (8.23)	57.08 (5.67)	-	51.15 (9.15)	-	$p<0.05$
Age of onset	20.95 (2.47)	21.73 (3.34)	-	23.56 (4.11)	-	NS
Age at institutionalization	45.78 (8.22)	49.34 (8.86)	-	42.22 (7.76)	-	$p<0.05$
Duration of illness	21.67 (9.33)	25.16 (7.56)	-	18.18 (8.54)	-	$p<0.05$
Patients with age below 40	40	12	8.00	28	16.2	$p<0.05$
Number of admission in 2 years period before institutionalization (mean)	-	6	-	7	-	NS
Type of schizophrenia						
paranoid	217	105	70.00	112	65.11	NS

disorganized	71	30	20.00	41	23.83	NS
undifferentiated	27	14	9.33	13	7.55	NS
other	7	1	0.66	6	3.48	NS
Place before institutionalization						
home	253	120	80.00	133	77.32	NS
hospital	50	20	13.33	30	17.44	NS
other	19	10	6.66	9	5.24	NS
Patient living						
alone	37	14	9.33	23	13.37	NS
with husband/wife	25	13	8.66	6.9	1.16	NS
with one parent	78	33	22.00	45	26.16	NS
with both parents	23	11	7.33	12	6.97	NS
with son/daughter	35	17	11.33	18	10.46	NS
with brother/sister	80	33	22.00	47	27.32	$p<0.05$
other	44	22	14.66	22	12.79	NS
Education						
1-4 years	45	23	15.33	22	12.79	NS
5-8 years	175	87	58.00	88	51.16	NS
9-12 years	80	33	22.00	47	27.32	NS
more than 12 years	22	9	6.00	13	7.55	NS

The Cox analysis for the middle aged sample showed that persons with schizophrenia aged 40–55 in 2005-2014 have 3.40 times the risk institutionalization compared with individuals of similar age in 1995-2004 period (table 3). Other risk factors for institutionalization among the middle-aged cohort are age (HR = 1.23), being female (HR = 1.45), and having only one parent (HR = 1.72). The patients living with brothers are at the higher risk for institutionalization.

Table 2. Cox Proportional Hazards Models of institutionalization

	Group A, 1995-2004		Group B, 2005-2014		P value
	(N = 150)		(N = 172)		
Variable	HR	95% CI	HR	95% CI	NS
Disorganized type	3.40	2.77–4.98	1.43	1.15–2.44	$p< 0.05$
Age (years)	1.11	1.08–1.12	1.23	1.11–1.15	NS
Charlson score >0	1.21	0.88–1.66	1.10	1.06–1.41	$p< 0.05$
Female	1.36	1.05–1.76	1.49	1.17–1.46	$p<0.05$

All the patients were treated with antipsychotics (table 3). The vast majority of patients received haloperidol, even if the second generation antipsychotic were available. There were few patients treated with clozapine before 1995. The treatment was not available, underutilized due to fear of agranulocitosis, mycoarditis and seizures.

Table 3. Treatment categories used in patients with schizophrenia

antipsychotics	All patients	discharged patients				*p* value
	322	1995-2004 (N=150)	%	2005-2014 (N=172)	%	
haloperidol	137 (42.54%)	67	44.66	70	40.69	NS
flupentixol	22 (6.83%)	12	8.00	10	5.9	NS
zuclopentixol	27 (8.35%)	17	11.00	10	5.9	NS
olanzapine	55 (17.08%)	23	15.33	30	17.44	NS
quetiapine	12 (3.72%)	5	3.3	7	4.12	NS
clozapine	33 (10.24%)	12	8.00	21	12.20	$p<0.05$
risperidone	23 (7.1%)	16	10.5	7	4.12	$p<0.05$
amisulprid	13 (4.1%)	6	4.00	7	4.12	NS

Our findings show that despite the relative reduction of hospitalization in acute settings there is a tendency of families to push institutionalization of patients with schizophrenia even if those patients are still young. There are some predictive factors which include: aggressive behavior, living with brother or sister, male gender and multiple admissions to the acute psychiatric units in short period of time. In the present days we noticed less time allocated by relatives to talk and spend time with schizophrenic patients. The main reason declared is the economic situation of those families.

Patients with schizophrenia requiring long-term institutionalization represent those with the worst outcome, leading to personal costs for patients and relatives and constituting a large economical burden for society [71].

Aggressive and disruptive behavior remained the reasons for admission in ,,acute settings,, in the current days. In the same time represents a major difficulty to discharge patient due to fear of violent behavior towards relatives. When aggressive behavior is accompanied by cognitive impairment the delay of discharge are even longer [72]. In a systematic study of aggression researchers found that the prevalence of aggression in long stay patients was equivalent to that seen in acutely admitted patients admitted within the last 3 days in earlier studies. Several studies show that negative symptoms are associated with aggressive behavior [73]. These negative symptom correlate results have been interpreted in terms of frontal lobe

dysfunction as alterations in emotional functioning are common in individuals with frontal lobe damage.The majority of the participants showed enhancements in social functioning despite the fact that functional impairment is common in persons with schizophrenia, which indicates that even long-stay patients could achieve better functioning by deinstitutionalization. Although the stability in symptoms might be due to continuous schizophrenia course, moving to the community may also lead to improvement [74]. A recent study indicates that hospital-based rehabilitation together with weekly supportive psychodynamic therapy was associated with a continued increased use of psychiatric bed days and days in supported housing [75].

Discharged patients had more leisure activities, more often a "good friend", and more frequent social contacts. They were less often victim of a crime within the last year. In a cross-sectional comparison, they were significantly more satisfied with their life than patients who were still in hospital [76]. Our study show that the number of patients who were discharged after institutionalization in period 1995-2004 was significantly higher compared with period 2005-2014.

Despite the access to LAIs there are a large number of patients who was institutionalized before treatment with a depot antipsychotic or clozapine. Clozapine as well as LAIs remained highly underutilized in patients with schizophrenia even if they are non-adherent or nonresponsive to other antipsychotics. In the vast majority of cases they were declared ,,schizophrenia treatment-resistant" but the evidence are for highly non-adherent to treatment patients.

Further studies are needed to demonstrate de beneficial of treatment with LAIs in prevention of institutionalization of young patients with schizophrenia.

Hospitalization for people with schizophrenia is a consequence of several different behavioral and social psychosocial factors. Middle-aged persons with schizophrenia have almost four times greater likelihood of early institutionalization in nursing homes compared with their same age peers with no mental illness. The chronic, highly debilitating and refractory nature of these disorders means that stabilization of an individual's condition regularly requires long stays in hospital and often for lifetime. Second generation LAIs can serve to prevent cognitive and functional decline in schizophrenia. Clozapine treatment has been shown in several studies to be efficient in treatment-resistant patients.

We concluded that continued efforts are needed to engage people with schizophrenia in treatment in order to prevent early institutionalization.

1.5 Cardiovascular and metabolic comorbidities in schizophrenia

Ifteni P, Correll CU, Burtea V, Kane JM, Manu P. Sudden unexpected death in schizophrenia: autopsy findings in psychiatric inpatients. Schizophr Res. 2014 May;155(1-3):72-6

The physical health of patients with schizophrenia is poor [77] and a large body of evidence has documented their shortened life expectancy [78, 79]. Suicides, accidents and cardiovascular disorders are considered the main reasons for the excess of premature, sudden and unexpected deaths in this population [80]. In patients treated with antipsychotic drugs, which include a large number of individuals receiving psychiatric care for schizophrenia, sudden cardiac death has been the focus of large epidemiological studies in the United States [81].

Using death certificates and complex algorithms to exclude patients who died from previously known noncardiac conditions and to adjust for co-morbid somatic disorders, the investigators established that the incidence-rate ratio of sudden cardiac death was doubled in individuals prescribed first- or second-generation antipsychotics in the last month of life. The findings were thought to reflect the dose-dependent antipsychotic drugs' inhibitory effect on phase 3 of the myocardial cell depolarization, which may lead to torsades de pointes, an arrhythmia that may lead to ventricular fibrillation and sudden death. However,the findings were disputed by the American Psychiatric Association's Council on Research, which has stated that "a retrospective analysis of death certificates to evaluate mortality by SCD [sudden cardiac death], may overestimate SCD incidence"[82]. The American Psychiatric Association's position is supported by the methodology used to ascertain the sudden arrhythmic death syndrome. This diagnosis is made in cases of sudden death with no history of cardiac disease, no identifiable macroscopic cause of death at a complete autopsy, and no abnormal findings on microscopic examination of the heart by a cardiac pathologist. Autopsy findings in patients with schizophrenia who died suddenly have been reported only a few times in the past two decades. In a study of 66 cases presented to the medical examiner in Maryland from 1994 through 1996, the majority of deaths not due to accidents or suicideswere caused by atherosclerotic heart disease [83]. In a10-year review of 683 autopsies performed in people with a history ofschizophrenia by the Department of Forensic Medicine in Sydney, Australia, the main cause of natural death was cardiovascular disease, present in 23% of a cohort in which 37% of deaths were attributedto suicide or voluntary

overdose with prescribed or illicit drugs. In a Australian study, 72 (11%) of cases remained unexplained, and 30 of these patients were presumed to have primary arrhythmogenic disorders which may have been discover a bleat a "molecular autopsy". A study limited to 10 cases of clozapine-induced myocarditis diagnosed at autopsy included 3 patients with sudden and unexpected death [84]. The significance of these observations is limited by selection bias and incomplete clinical data.

In this study, we present analyses of a consecutive cohort of patients treated for schizophrenia who died suddenly and unexpectedly in Romania, a country in which the public health legislation mandates autopsies for all patients dying during a hospital stay. We adopted a null hypothesis and postulated that the main cause of death in patients with schizophrenia is no different than in the general population, i.e., coronary artery disease with evidence of acute myocardial infarction. The patients described in this report were admitted to a 120-bed, free standing, public psychiatric hospital located in Brasov, Romania (population 277,000). The clinical care is provided by board certified psychiatrists affiliated with the local medical school. Patients deemed by their treating psychiatrist to have a significant medical deterioration are transferred the same day to the county hospital. The retrospective review of medical records was approved by the hospital's Ethics in Research Committee. From January 1, 1989 through December 31, 2011, the hospital admitted 7189 adult patients diagnosed with schizophrenia according to the contemporaneous version of the Diagnostic and Statistical Manual of the American Psychiatric Association. Public health legislation requires a forensic evaluation of all inpatient deaths. The post-mortem examinations are carried out by board certified pathologists employed by the government at the local Institute for Legal Medicine. Autopsies are performed in all cases and the pathology report must include a summary of the findings. Exceptions from autopsy are granted only for narrowly defined religious or personal preference reasons.

Hospital records over the 25-year period of the study identified 57 patients who died suddenly and unexpectedly. All of these patients died while being asymptomatic or within 1 h of new symptom(s) onset. None of these patients died of physical trauma, homicide, suicide or accidental drug overdose.

Autopsies were performed in 51 (89.5%) of the 57 patients with schizophrenia who died suddenly and unexpectedly. Data extracted from their medical records and the post-mortem examination report included demographic information, duration of psychiatric disorder, length of stay prior to death, past medical history, medication regimen at the time of death,

and autopsy findings. The chlorpromazine equivalent of the antipsychotic drugs received in 24 h preceding the sudden death was calculated according to published guidelines.

The study group comprised 29 males (56.9%) and 22 females (43.1%) with a mean age of 55.9 ± 9.4 years (Table 1). Patients had been diagnosed with schizophrenia for an average of 27.7 ± 10.3 years prior to their sudden death. The admitting diagnosis for the last hospitalization was paranoid subtype in 47 patients (92.2%), and catatonic and undifferentiated in 2 patients (3.9%) each. With the exception of one patient with pneumonia in whom the antipsychotic was stopped 2 days prior to death, all patients had received antipsychotic drugs in 24 h preceding their death, which had occurred after an average length of stay of 11.7 ± 7.6 days. The past medical history, as recorded by the admitting psychiatrists, was remarkable for congestive heart failure (4 patients, 7.8%), arterial hypertension (4 patients, 7.8%), bronchial asthma or chronic obstructive pulmonary disease (3 patients, 5.9%), diabetes mellitus (1 patient, 2.0%) and dyslipidemia (1 patient).

Causes of death

Cardiovascular disorders, identified in 32 (62.8%) of the cases, were the most common cause of sudden death in this cohort of inpatients with schizophrenia. The cardiovascular disorders included 27 patients (52.9%) with acute myocardial infarction, and 3 patients (5.9%) with myocarditis. None of the cases of myocarditis had been treated with clozapine. One patient (2.0%) had dilated cardiomyopathy and acutely decompensated heart failure with pulmonary edema. The cause of death was identified in one patient (2%) as cardiac tamponade due to hemopericardium. This patient was the only one restrained just before the sudden death. He had a ruptured left ventricular wall, and may have had an early myocardial infarction, but the report of microscopic findings could not be located for this retrospective analysis. Among the 11 (21.6%) patients who died of a respiratory disorder, 6 (11.8%) had pneumonic consolidations, 4 (7.8%) had airway obstruction (laryngeal or tracheal) with food boluses, and one (2.0%) died of a massive pulmonary embolus. In two cases (3.9%), the death was due to a neurological disorder, a hemorrhagic stroke and a brain tumor (Table 2).

The post-mortem macroscopic and histological examination did not identify a specific cause of death in 6 (11.8%) patients. Structural abnormalities of the heart were identified in 5 of them, i.e., extensive coronary arteriosclerosis in 3, dystrophic myocardial changes and chronic pericarditis in one patient each (Table 3). The patients with coronary atherosclerosis had no evidence of coronary thrombosis or myocardial necrosis. The patient with myocardial dystrophy had fibrofatty replacement, similar to findings reported in cases of sudden death produced by arrhythmogenic cardiomyopathy, but no pre-mortem evidence of ventricular

rhythm disturbance. No additional virological, toxicological or biochemical studies were performed.

Table 1
Demographic features and psychotropic drug treatment of schizophrenia inpatients who died suddenly and unexpectedly and had a post-mortem examination.

Characteristic	Total (N = 51)	Myocardial infarction on autopsy (N = 27)	No myocardial infarction on autopsy (N = 24)	p
Age (years ± S.D.)	55.9 ± 9.4	53.9 ± 9.0	58.3 ± 9.9	0.10
Male gender, N (%)	29 (56.9%)	16 (59.3%)	13 (54.2%)	0.71
Duration of schizophrenia (years ± S.D.)	27.7 ± 10.3	25.6 ± 10.0	30.1 ± 10.5	0.13
Length of stay (days ± S.D.)	11.7 ± 7.6	10.5 ± 7.0	13.0 ± 8.2	0.26
Antipsychotic drugs at the time of death, N (%)				
First generation antipsychotics	43 (83.4%)	23 (85.4%)	20 (83.3%)	0.85
Haloperidol	38 (74.5%)	19 (70.4%)	20 (83.3%)	0.28
Levopromazine	19 (37.3%)	9 (33.3%)	10 (41.7%)	0.54
Chlorpromazine	5 (9.8%)	4 (14.8%)	1 (4.2%)	0.20
Thioproperazine	2 (3.9%)	2 (7.4%)	0	0.17
Second generation antipsychotics (%)	8 (15.7%)	4 (14.8%)	4 (16.7%)	0.85
Clozapine	3 (5.9%)	1 (3.7%)	2 (8.3%)	0.48
Amisulpride	3 (5.9%)	2 (7.4%)	1 (4.2%)	0.62
Olanzapine	1 (2.0%)	1 (3.7%)	0 (0.0%)	0.25
Quetiapine	1 (2.0%)	0 (0.0%)	1 (4.2%)	0.28
Number of antipsychotic drugs ± S.D.	1.43 ± 0.58	1.41 ± 0.64	1.46 ± 0.51	0.76
Antipsychotic polytherapy, N (%)	20 (39.2%)	9 (33.3%)	11 (45.8%)	0.36
Chlorpromazine equivalent (mg/day ± S.D.)	420.1 ± 187.1	410.2 ± 198.3	431.3 ± 173.6	0.69
Other psychotropics at the time of death, N (%)				
Benzodiazepines	38 (74.5%)	19 (70.4%)	19 (79.2%)	0.47
Mood stabilizers	18 (35.3%)	12 (44.4%)	6 (25%)	0.15
Antidepressants	2 (3.9%)	0 (0.0%)	2 (8.3%)	0.13

Patients who died of myocardial infarction (n = 27) and those who died of another cause (n = 24) were similar with regard to age, gender, duration of illness, length of stay, psychotropic treatment during their last admission (Table 1) and past medical history. A majority of patients in both groups were cigarette smokers (63.0% vs 66.7%, p = 0.78). The groups with and without myocardial infarction had similar bodymass index (25.0 ± 3.3vs.25.9± 4.5 kg/m2, p = 0.40) and proportion of patients with fasting glucose levels ≥100 mg/day (18.5% vs. 16.7%, p = 0.86). Low-density lipoprotein cholesterol levels were not assessed.

Table 2
Causes of sudden, unexpected death in schizophrenia inpatients who had a post-mortem examination.

Cause of death	N (%)	95% confidence interval
Cardiovascular disorders	32 (62.8%)	49.5–76.0%
Myocardial infarction	27 (52.9%)	39.2–66.6%
Myocarditis	3 (5.9%)	0–12.3%
Dilated cardiomyopathy	1 (2.0%)	0–5.8%
Hemopericardium	1 (2.0%)	0–5.8%
Respiratory disorders	11 (21.6%)	10.3–32.9%
Pneumonia	6 (11.8%)	2.9–20.6%
Airway obstruction	4 (7.8%)	0.5–15.2%
Pulmonary embolus	1 (2.0%)	0–5.8%
Neurological disorders	2 (3.9%)	0–9.2%
Hemorrhagic stroke	1 (2.0%)	0–5.8%
Brain tumor	1 (2.0%)	0–5.8%
Unexplained	6 (11.8%)	2.9–20.6%

In this study, we used autopsy findings to determine the cause of sudden death in a cohort of 7189 patients admitted for the treatment of schizophrenia to a free standing teaching psychiatric hospital over a 25-year period (1989–2013). Medical record review identified 57 (0.79%) patients who died suddenly and unexpectedly during the hospital stay. Autopsies were performed in 51 patients. The post-mortem examinations indicated that 27 (52.9%) patients had myocardial infarction, 6 (11.8%) pneumonia, 4 (7.8%) airway obstruction, 3 (5.9%) myocarditis, and 1 (2.0%) each dilated cardiomyopathy, hemopericardium, pulmonary embolus, hemorrhagic stroke and brain tumor. The sudden death remained unexplained in 6 (11.8%) patients, 3 of whom had evidence of coronary arteriosclerosis on autopsy. Patients with and without myocardial infarction were similar with regard to age, gender, smoking, body mass index and psychotropic drug therapy. The rate of myocardial infarction identified in this study is greater than that in community samples and, if confirmed in larges samples of patients with schizophrenia, may represent a specific vulnerability of patients with this psychotic disorder.

Table 3
Demographic features and autopsy findings in schizophrenia patients with unexplained sudden death.

Patient #	Age (years)	Gender	Body mass index	Smoker	Length of stay (days)	Autopsy findings
1	32	Male	29.0	Yes	11	Interstitial pulmonary fibrosis
2	49	Male	20.1	Yes	6	Coronary arteriosclerosis
3	60	Male	27.3	Yes	10	Myocardial dystrophy
4	66	Male	32.7	Yes	6	Coronary arteriosclerosis
5	58	Female	21.1	Yes	2	Coronary arteriosclerosis
6	66	Female	25.5	No	4	Chronic pericarditis

The data are limited by the lack of toxicological evaluation of cases without a clear cause of death, incomplete pre-mortem assessments of risk factors for coronary artery disease, and absence of information regarding the prevalence and etiology of sudden death in the community from which the psychiatric hospital receives its patients. Nevertheless, this is the first study in which all sudden deaths in patients with schizophrenia have been witnessed and an autopsy was carried out without delay in a near-totality (89.5%) of cases. The autopsy findings support the hypothesis that the causes of sudden death in schizophrenia are not different than in the community-dwelling populations [85] and patients admitted to general hospitals without severe mental illness, in whom unexpected deaths are primarily due to coronary artery disease that has produced a myocardial infarction. Coronary artery disease is highly prevalent as a cause of sudden death (42%) even in subjects aged 30–40 years old. Advances in genetic testing aimed at discovering mutations associated with the long QT syndrome have not changed the etiological hierarchy of sudden death, as demonstrated by a recent study of 71 patients aged 25–60 who died suddenly in Minneapolis [86]. Acute coronary lesions were found in 27% of patients and previous silent myocardial infarction was

discovered in 34% of cases, while only 5 subjects (7%) had possibly deleterious mutations of the ion channel genes. The data generated by the autopsies in this cohort of patients with schizophrenia expand the observations previously reported by us on 100 consecutive sudden deaths (18% with autopsy) in psychiatric patients in a New York psychiatric institution [87]. Using structured, multidisciplinary root cause analyses, the cause of death was identified in 48 cases (48.0%). Fifteen of those (31.3%) had evidence of an acute coronary syndrome, while the unexplained cases were predicted by the presence of diabetes and dyslipidemia, i.e., the main risk factors for coronary artery disease. The utilization of antipsychotic drugs was similar in the explained and unexplained groups, a finding echoed by the finding of similar chlorpromazine equivalent dosages of antipsychotics administered during the last day of life to patients with and without myocardial infarction presented in our current report. Likewise, the other causes of death discovered at autopsy in this study were not different from those frequently reported in our previous survey of psychiatric patients in which we have found a similar prevalence of myocarditis, upper airway obstruction, pneumonia, pulmonary embolization and hemorrhagic strokes.

The one case of sudden death caused by rapidly expanding brain tumor is unusual and the proposed mechanism of death includes herniation due to mass effect, acute hemorrhage and seizures. Taken together, the data do not support a construct implying that an antipsychotic-related arrhythmia is the primary event responsible for a significant proportion of sudden deaths in patients with schizophrenia receiving antipsychotic drugs. The presence of upper airway obstruction with undigested food (choking) among the causes of death in this group of schizophrenia patients reflects the high risk of dysphagia in patients with severe mental illness. In a 400-bed Massachusetts hospital 4 patients died in 1 year from asphyxia. Prospective studies have identified bradykinetic dysphagia secondary to neuroleptic-induced extrapyramidal syndrome and fast eating syndrome as the most common causes of life-threatening choking episodes. The risk of deep venous thrombosis, leading to pulmonary embolism, is also increased in patients treated with antipsychotic drugs [88]. Our findings suggest that a substantial decrease in the prevalence of sudden death in schizophrenia can be obtained only through programs aimed at the primary prevention of coronary artery disease and secondary prevention of myocardial infarction. In the Framingham Heart Study, from 1950 to 1999, such programs have proven their effectiveness among individuals without psychotic disorders by decreasing the risks of sudden death and non-sudden mortality related to coronary artery disease by 49% and 64%, respectively. Reductions of this magnitude will require not only early detection and treatment of coronary and diabetogenic risk factors in

psychiatric settings, but also parity in access and quality of medical care for patients with schizophrenia. In order to achieve these important goals that have been highlighted for at least a decade now, provider, patient and system level barriers must be identified and addressed [89].

1.6 Dilemma of treating schizophrenia during pregnancy

1.6.1 Eficacy and safety of antypsychotcs during pregnancy

The choice of antipsychotic treatment during pregnancy remains subject to controversy, mainly due to a lack of exposure and outcome data that would allow for a meaningful risk estimate [90]. The current literature on antipsychotic use during pregnancy and breastfeeding are mostly found in case reports. Information regarding the safety of antipsychotic use during pregnancy is limited, creating a strong ethical dilemma [91]. Most data are available from observational and retrospective studies or isolated case-reports [92]. Prescribing psychotropic medications during pregnancy is a complex issue involving the assessment of the risk of leaving a severe psychiatric illness untreated with the attendant risk of complications to the mother and, thereby, indirectly to the born baby versus the risk of teratogenic/embryo-lethal effects on the developing fetus [93, 94]. Most second-generation antipsychotics have been used since the 1990's. Olanzapine is placed among category C drugs by the US Food and Dug Association *(i.*e., "Risk cannot be adequately ruled out. Animal and human studies have shown an adverse effect (i.e., teratogenic or embryo-lethal), but there are no adequate human studies") and there is no unequivocal evidence of harm to the fetus [95].

None of second generation antipsychotics (SGAs), including olanzapine, hold a licensed indication for treatment during pregnancy.

Our case reports describe three cases of closely monitored female patients with schizophrenia who were treated with olanzapine during pregnancy. We obtained written informed consent for publication from all patients before submission.

CASE 1

This report is about a 31-year old female patient, married for 4 years, university graduate, diagnosed with schizophrenia since the age of 21. She had previous psychiatric hospitalizations after stopping olanzapine treatment. The last psychiatric admission was in 2011. She agreed treatment with olanzapine LAI 300 mg once/month with excellent outcome for almost 4 years. In February 2014 the patient refused LAI arguing that had "enough with injections". She agreed to continue with oral olanzapine 10 mg/day. In May 2014, the patient appeared to the psychiatrist, requesting counseling and psychiatric treatment. The psychiatric evaluation at that time revealed mild anxiety, absence of psychotic symptoms and a very good level functioning. The patient asked about the possibility of becoming pregnant under treatment and also about genetic transmission of the psychiatric disease. The next evaluation was in September 2014 when she declared that she was 16 weeks pregnant, and that she continued the treatment with olanzapine 10 mg/day and escitalopram 10 mg/day until the day

before the consultation. Considering the current status and the patient's wish to keep the pregnancy, the decision was made to continue olanzapine treatment. She was monthly monitored throughout a private obstetric setting.

Monthly psychiatric evaluations through telephone with the patient and her husband showed a good and sustained remission. She gave birth by a Caesarean section to a normal healthy male child. The weight of the newborn was 3000 g. Both she and her husband declared that the infant, now 2 years old, had a normal development.

CASE 2

This report is about a 30 year old female diagnosed with schizophrenia since the age of 21 living with her mother and two normal brothers. The patient's medical history revealed the bipolar disorder diagnosis of her mother and the trauma caused by her parent's divorce at the age of 12. She experienced multiple relapses due to lack of insight and consecutive noncompliance to treatment. The "revolving door" included almost all antipsychotics, FGAs (First Generation Antipsychotics) and SGA (Second Generation Antipsychotics) even clozapine for a false treatment resistant schizophrenia (TRS).

In 2011, after a long and severe psychotic episode, the patient and her family agreed to undergo treatment with olanzapine long acting injectable (LAI) 300 mg twice/month. The patient's evolution was spectacular with no relapses during a 4-5 years period. She started to work in a small store and she became socially involved. In December 2015 the patient informed the psychiatrist upon her decision to continue treatment with oral olanzapine 10 mg/day instead of LAI. She was appointed monthly and evaluated by a board certificated psychiatrist and she continued treatment with olanzapine 10 mg/day and zopiclon 7.5 mg/day for insomnia.

The treatment was supervised during pregnancy by the family. She gave birth naturally to a normal female child (2800 grams, Apgar score=9). She was discharged after one week from Obstetrics Department and she continued treatment with olanzapine 10 mg/day.

CASE 3

It is about a 33-year old female diagnosed with schizophrenia since the age of 20. The patient history revealed frequent episodes of violence especially towards her mother. In 2011 she started olanzapine LAI 300 mg twice/month. Her psychopathological status was very much improved, with very good functioning compared with pre-LAI period including a call-center job and a boyfriend. In September 2015 she decided to stop LAI and continued oral treatment for 2 more months then totally stopped medication. In February 2016 she was admitted in our emergency psychiatric unit after a violent conflict with her mother. She presented delusion of

persecution, agitation and hostility. She was treated with olanzapine 10 mg BID and oral lorazepam 1 mg BID. After a routine investigation we noticed that she was 25 weeks pregnant. Initially for safety reasons and then as consequence of a legal order (she was accused for physical violence by her mother and a judge decided a long term hospitalization) she remained in a psychiatric acute setting during pregnancy. She was monthly monitored by an obstetrician. In August 2016 she was transferred to the Obstetrics and Gynecology Department and she gave birth by Caesarian section to a 3300 g male child, apparently healthy.

Two months later the new born and his mother were well. The patient was in remission and she continued treatment with olanzapine 10 mg BID in hospital until the final legal decision.

This small consecutive case series demonstrate that patients with schizophrenia can be treated with olanzapine during pregnancy. Women with psychiatric conditions may become pregnant especially in the situations of lack of insight or social support. In the case of second-generation antipsychotics, there are no routine treatment recommendations applied during pregnancy, and it is difficult to reach definitive conclusions regarding their safety for the developing child. The patients were previously treated with olanzapine LAI with very good improvement and then they decided to stop treatment due to injectable formulation.

Our case reports describes three cases of female patients with schizophrenia who continued oral treatment with olanzapine during pregnancy. It is very plausible that two of them were on treatment since week 1 of pregnancy (family statement and supervision) in a remission phase, and one from week 25, when she was admitted for relapse. The newborn babies were age appropriately developed. In the first case, it was an intended pregnancy, while in the other cases pregnancy occurred accidentally.

In our previous case report [96] we showed that olanzapine was safe for the new born when it was taken in first trimester. At the same time, the patient relapsed when stopped medication after week 20 of pregnancy.

In a recent paper, from 610 pregnancies exposed to olanzapine there were 66% normal births, 9.8% premature births, 9.3% spontaneous abortions, 8% perinatal conditions and 4.4% congenital anomalies which did not appear to be an increased risk compared with the general population.

FDA (The Food and Drug Administration) classify medication risk during pregnancy into five categories to inform clinicians about the risks of fetus exposure. Categories include A (no risk in well-controlled human studies), B (no risk in animal studies), C (adverse effect on the fetus in animal studies, but no adequate studies in humans and potential benefits may

warrant use of the drug in pregnant women despite potential risks), D (adverse effect on the fetus in animal studies and human investigational or marketing experience, but potential benefits may warrant use of the drug in pregnant women despite potential risks), and X (adverse effect on the fetus in animal studies and human investigational or marketing experience, and risks clearly outweigh potential benefits). Congenital defects like meningocele or ankyloblepharon, hip dysplasia, acheiria, and cardiovascular defect, have been reported in children previously exposed to olanzapine in utero.

The American Congress of Obstetricians and Gynecologists based on the available data of risks and benefits, recommends continuing pharmacotherapy during pregnancy as severe psychiatric episodes are generally thought to be caused by discontinuation of medication. In the same time, a psychotic mother can also affect the health of the fetus.

Olanzapine was found to be associated with low birth weight in a dose-dependent manner.

Findings from 23 prospectively olanzapine-exposed pregnancies showed a 13% rate of spontaneous abortion, 5% stillbirth, 0% major malformations, and 5% prematurity, all within the range of normal control rates [97].

Another study of 18 pregnancies provided similar results, suggesting that olanzapine was relatively safe when used during pregnancy [98]. There was also one case report suggesting that the use of olanzapine during pregnancy was associated with neonatal hypoglycemia due to hyperinsulinemia [99] unconfirmed in our cases where the glucose level was normal, while insulin levels had not been taken (not mandatory in the local protocol).

The weights of all 3 newborns were 2800 g (girl), 3000 g and 3300 g (boys) considered as normal weight. Higher rates of low birth weight (LBW), defined as a birth weight of a liveborn infant of less than 2,500 g regardless of gestational age and neonatal intensive care unit admission were reported in cases with olanzapine exposure during pregnancy compared with mothers who were treated with other atypical antipsychotics.

In another systematic review, authors evaluated 1090 first-trimester-exposed pregnancies with 38 malformations resulting in a malformation rate of 3.5% concluded that first-trimester exposure to olanzapine was not associated with an increased risk of congenital malformation [100].

In conclusion, the available data suggest that olanzapine can be used as first-line drug during first-trimester pregnancy. Other maternal factors relevant for the choice of an antipsychotic such as drug-specific adverse effect profile, previous response, weight gain, gestational diabetes, patient preference and drug availability must be taken into acount.

These data may be useful to help guide clinicians and women decide to continue, or discontinue, olanzapine therapy during pregnancy, but should be considered within the limitations associated with limited data. Women should notify their clinicians if they become pregnant or intend to become pregnant while being treated with olanzapine or other psychotropics.

There are no controlled studies for the use of olanzapine therapy in pregnant women. More studies are needed to determine the effects of antipsychotics, including olanzapine, on pregnant women and the developing fetus. Schizophrenia relapse during pregnancy may expose the mother and the fetus to high risk if olanzapine is stopped. It is important to assess the risks and benefits of treating pregnant or breastfeeding women with antipsychotics, and weigh these against possible risks of anomalies and developmental problems to the fetus or child.

1.6.2 Stopping treatment during pregnancy-a major risk for mother and child

Ifteni P, Moga MA, Burtea V, Correll CU. Schizophrenia relapse after stopping olanzapine treatment during pregnancy: a case report. Ther Clin Risk Manag. 2014 Oct 23;10:901-4

Information regarding the safety of antipsychotic drug use during pregnancy is limited, creating a strong ethical dilemma [101]. Most data are available from observational studies and isolated case reports [102]. Prescribing psychotropic medications during pregnancy is a complex issue. It involves the assessment of the risk of leaving a severe psychiatric illness untreated with the attendant risk of complications to the mother and, thereby, indirectly to the newborn baby, versus the potential risk of teratogenic/embryo-lethal effects on the developing fetus [103,104]. Most second-generation antipsychotics have been used since the 1990s. Olanzapine is placed among category C drugs by the US Food and Drug Administration (ie, "Risk cannot be adequately ruled out. Animal studies have shown an adverse effect [ie, teratogenic or embryo-lethal], but there are no adequate human studies"), and there is no unequivocal evidence of harm to the fetus [105].

The present case report focuses on a female patient diagnosed with schizophrenia who was undergoing treatment with olanzapine and valproic acid during the first and half of the second trimester of pregnancy, and who was psychiatrically hospitalized for a schizophrenia relapse 16 weeks after having stopped olanzapine. The day after the admission, she gave birth by a Cesarean section to a healthy male child. The patient provided written consent for the anonymous publication of her case

This report is about a 28-year old female patient, married for 2 years, a university graduate, and diagnosed with schizophrenia from 19 years old. She had four previous psychiatric hospitalizations in Romania and abroad, and had a suicide attempt at age 21, overdosing on olanzapine. The last psychiatric admission was in 2012, again for a schizophrenia relapse. During that hospitalization, the patient was treated with olanzapine 20 mg/day, diazepam 40 mg/day and valproic acid 900 mg/day, with fast remission of the psychotic symptoms. At discharge, the patient was recommended to continue treatment with olanzapine 10 mg/day and valproic acid 1,000 mg/day, as well as ongoing outpatient care. Since the patient was married and sexually active, she was advised at every meeting with the psychiatrist regarding contraceptive methods and the risk of psychotropic treatment for a potential pregnancy.

In April 2013, the patient presented to the psychiatrist, requesting counseling and psychiatric treatment. The psychiatric evaluation at that time revealed marked irritability, insomnia, and

persecutory delusions. The patient also shared for the first time with a health professional that she was 13 weeks pregnant, and that she had continued the treatment with both olanzapine 10 mg/day and valproic acid 500–1,000 mg/day until the day before the consultation. Considering the current status and the patient's wish to continue with the pregnancy, the decision was made to continue olanzapine treatment, but to discontinue valproic acid due to its potential to cause neural tube defects. The plan and further evaluations were accompanied by discussions with the patient's gynecologist and primary care physician. Further psychiatric evaluations showed an improvement in the patient's status with continuation of olanzapine 10 mg/day.

At week 21 of the pregnancy, however, during psychiatric evaluation, the patient affirmed that she stopped taking olanzapine 1 week ago because "she felt well'' and because she did not like the associated weight gain and daytime sedation. She was psychiatrically stable 1 week after having discontinued olanzapine and was periodically evaluated at the outpatient department, while the pregnancy progressed normally, documented by ultrasound measurements.

In October 2013, at 36 weeks of pregnancy and 16 weeks after having stopped taking olanzapine, the patient was admitted to the psychiatric emergency unit, presenting with marked psychomotor agitation, incoherence, persecutory delusions, insomnia, mood lability, and marked dysphoria. Biological investigations showed mild anemia (hemoglobin 11.9 g/dL, haematocrit 34.8%), macrocytosis, mild hypercholesterolemia (221 mg/dL), and an aspartate aminotransferase (serum glutamate oxaloacetate transaminase) of 34 U/L with normal fasting glucose value. She was treated with diazepam 40 mg over a period of 12 hours, and then transferred to an obstetrics hospital where she gave birth by Cesarean section to a boy. At birth, the health status of the new born child, including glucose levels (80 mg/dL), was normal (insulin was not assessed). In the obstetrics department, she was treated with haloperidol short-acting injectable 5 mg/day and diazepam as needed for severe agitation and psychotic symptoms according to the psychiatrist's recommendation and to the hospital protocol, with mild improvement of symptoms. Lactation was suppressed with bromocriptine 5 mg/day and she was discharged after 1 week.

After discharge, she continued treatment with haloperidol 10 mg/day, valproic acid 1,000 mg/day, and tryhexifenidyl 4 mg/day with worsening of psychotic symptoms due to partial non-compliance.

One month after the birth, the patient was re-admitted to the psychiatric hospital for restlessness, insomnia, and persecutory and grandiose delusions. During this admission, the

patient was initially treated with haloperidol 10 mg/day, but she started to present parkinsonian symptoms despite lowering the dosage and adding anticholinergic medication. The patient refused re-initiating treatment with olanzapine due to previous increased body weight and severe daytime somnolence. The psychiatrist decided to restart amisulpride, based on a good therapeutic response a few years ago and less risk for weight gain and sedation. The decision was agreed upon by the patient and her husband. Biological investigations showed a mildly lower value of hemoglobin (11.7 g/dL), but a normal value of hematocrit and no morphological abnormalities of the red blood cells. Blood glucose and cholesterol values were within normal range. The treatment recommended at discharge was amisulpride 600 mg/day, valproic acid 1,500 mg/day, diazepam 10 mg/day, and tryhexiphenidyl 2 mg/day. After discharge, the patient was monitored as an outpatient and continued with the treatment as recommended.

Since April 2014, the patient has remained in clinical remission. Both she and her husband declared that the infant, at 6 months of age, has been developing normally so far, both physically and psychologically. No formal assessment by a pediatrician was available.

In the case of second-generation antipsychotics, there are no routine treatment recommendations for their use during pregnancy, and it is difficult to reach definitive conclusions regarding their safety for the developing child. Our case report describes a female patient with schizophrenia who continued treatment with olanzapine during pregnancy from week 1 until week 20 when she stopped all medications herself. Subsequently, she relapsed at week 36 when she was hospitalized for 12 hours in the psychiatric hospital and then transferred to the obstetrics department where she gave birth to a healthy boy by Cesarean section. The newborn baby was normally developed for his age. The patient and baby were discharged after 2 weeks.

Clinicians must weigh the relative risks of medications administered during pregnancy and the associated risk of relapse if pharmacologic treatment is discontinued. The relapse of this patient with schizophrenia within 4 months of stopping her antipsychotic was an expected event. A recent meta-analysis of six trials showed that 77% (range: 57%–91%) of first episode schizophrenia patients who are randomized to discontinue antipsychotics relapsed compared to 3% of the patients randomized to continue antipsychotics. According to a large meta-analysis, placebo controlled discontinuation trials demonstrated that relapses start early after replacing antipsychotic treatment with placebo, with 37.2% of patients experiencing a relapse within the first 3 months. For women who are required to continue antipsychotic treatment during the first trimester, the lowest effective dose of a medication must be used,

and agents with the lowest teratogenic potential should be selected. The US Food and Drug Administration classify medication risk during pregnancy into five categories to inform clinicians about the risks of fetus exposure. Categories include A (no risk in well-controlled human studies), B (no risk in animal studies), C (adverse effect on the fetus in animal studies, but no adequate studies in humans and potential benefits may warrant use of the drug in pregnant women despite potential risks), D (adverse effect on the fetus in animal studies and human investigational or marketing experience, but potential benefits may warrant use of the drug in pregnant women despite potential risks), and X (adverse effect on the fetus in animal studies and human investigational or marketing experience, and risks clearly outweigh potential benefits).

Based on the available evidence of risks and benefits, the American Congress of Obstetricians and Gynecologists recommends continuing pharmacotherapy during pregnancy because severe psychiatric episodes are generally thought to be caused by discontinuation of medication, and an ill mother also affects the health of the fetus. Various outcomes have been reported after olanzapine exposure during pregnancy. Olanzapine was found to be associated with low birth weight in a dose-dependent manner. Outcomes from 23 prospectively ascertained olanzapine-exposed pregnancies showed a 13% rate of spontaneous abortion, 5% stillbirth, 0% major malformations, and 5% prematurity, all within the range of normal historic control rates. Another study of 18 pregnancies yielded similar results, suggesting that olanzapine is relatively safe when used during pregnancy [106]. There is also one case report suggesting that the use of olanzapine during pregnancy is associated with neonatal hypoglycemia due to hyperinsulinemia, but in this case report glycemic levels were normal, while insulin levels had not been taken.

In another case report, the authors documented major complications, such as microcephaly and congenital anopthalmia after olanzapine exposure during the entire pregnancy. Kirchheiner reported a case of a woman with schizophrenia who gave birth to a healthy child after she was treated with olanzapine from the 18th week of gestation through to delivery .Treatment planning is critical for minimizing the risk to the mother and fetus while limiting the morbidity from active psychiatric illness. In order to assist patients in making the best choices for the health of the mother and fetus, clinicians must be familiar with the latest reproductive safety research of any medications used to treat the disorder.

1.7 Ethics of treatment in early psychosis

Ifteni P, Burtea V, Szalontay AS, Moga MA. Ethics of treatment in early psychosis. Revista Română de Bioetică, Vol. 13, Nr.3, july - september 2015

Clinicians who treat patients with schizophrenia often encountered ethical issues related to psychiatric treatment. Schizophrenia is a severe mental disorder frequently accompanied by cognitive impairment [107]. These impairments with psychotic symptoms and lack of insight, can affect the abilities of the patients to make fully informed decisions about their own mental care. In these cases, ensuring that consent for treatment is informed, voluntary and competent can become a difficult achievement [108]. Informed consent, as a core of these ethical principles, represents the expression of individual rights in both clinical and research contexts.

Ethics is a discipline that evaluates in order to understand the moral aspects of human nature and action [109]. One of the major issues in the ethics of schizophrenia includes a relatively low prevalence of disorder but with a potentially devastating effect on the person life and with a critical effect on their families. After onset, untreated schizophrenia may be followed by loss of productivity and high costs for the community, often may be present through lifetime.

There is undeniable evidence that demonstrates that many patients have difficulty receiving psychiatric treatment after the onset of symptoms of schizophrenia. Delay of treatment can profoundly affect the future development of the patient, representing a major burden for family.

Regarding therapeutic research, there are neurobiological aspects as fundamental basis in the establishment of various types of therapeutic intervention. As known, characteristic schizophrenic changes process probability starts in the womb, the result of the interaction of multiple factors, such as genetic defects, trauma factors, infectious, immune and stress.

The way to achieve mental health is often long and sinuous, in particular for psychotic disorders. Recent studies on patients at first episode of schizophrenia have shown that the average duration between the onset of symptoms and initiation of treatment is over two years and where this term was three years are not exceptional [110]. Moreover, early but nonspecific signs such as mood disorders, suicidal ideation and impaired concentration may occur even ten years before the onset of psychotic symptoms [111]. Neurodegenerative theory involves behavioural and cognitive deterioration of the disease. Cognitive deficits

have a highly significant psychopathology when they are used and included in long-term prognosis of the disease. Therefore, these deficits are also a target of the current pharmacological therapies, accepting the idea that they can have a major impact on compliance therapy. Likewise all benchmarking showed a strong correlation with negative symptoms of cognitive impairment in schizophrenia, and the poor results of neuropsychological tests were obtained from patients with focal brain lesions.

Ethnic groups, social and economic status, high levels of negative symptoms, personality disorders may be factors affecting prognosis and disease progression.

Accurate and comprehensive assessment of onset of symptoms made by an experienced psychiatrist and early initiation of treatment, constitute decisive factors in the evolution and prognosis of patients with schizophrenia. Pharmacological intervention in schizophrenia is to cure specific symptoms of the illness and prevent psychotic relapses. These two objectives are plausible if they are made early at the onset of the disease. Moreover, it is known that schizophrenia is an enduring psychopathological process within which the early stages are the most active, aggressive and significance for the further development of the patient. Another dimension of pharmacological treatment is conservation cognitive and affective fund.

The biggest challenge is such as early recognition of symptoms of disease while minimizing the risk of false diagnosis.

It is possible to consider that treatment in early stages of schizophrenia may be intrusive and sometimes invasive due to patient’s lack of insight. Even test for differential diagnostics are difficult to be accomplished.

The average duration of prodromal symptoms before the onset of psychotic symptoms may be 2 years (women have a shorter prodromal period). Time to initiation of antipsychotic treatment is about three years, depending on the tolerance level of the community to substantial levels of psychopathology [112]. During the prodromal phase, 80% of patients have depression and social decline and stagnation in personality development begins even before the first hospitalization [113].

The onset of schizophrenia frequently occurs at teenagers. This is a critical period with an increased risk of developing psychotic disorders, especially in vulnerable people. Neuroimaging techniques have made it possible to reveal the changes in brain structure puberty.

Unfortunately for long-term prognosis of the disease, many of the symptoms of the prodromal phase of schizophrenia with onset in adolescence are misinterpreted by parents, teachers, and relatives as "a passing phase of adolescence". However, the approach of

identifying schizophrenia is not easy given the non-specificity of symptoms in the prodromal phase. This is why the assessment of potential indicators for schizophrenia is taken into accounts both the objective neuropsychological deficits and the subjective self-perception.

Abnormalities in information processing could play an important role in identifying prodromal states of psychosis and predict the probability of transition to, thus forming the neuropsychological markers. Disruption of attention has been described as one of the strongest markers of susceptibility for schizophrenia in research on high-risk individuals for schizophrenia [114], with verbal fluency tests that have proven to be the neuropsychological indicator for deficit with more sensitive performance [115].

In the clinical setting it is a legal and ethical obligation for clinicians to inform patients about the patient's illness and alternatives for care and assist them in making decisions about treatment. In the research setting the investigators must inform participants about the research protocol and help them understand the purposes, risks and benefits.

In schizophrenia, disability justifies involuntary internment and involuntary treatment as a significant reduction in ethical freedom. The absence of the conscience of the disease is a cognitive disability justifying the intervention in those circumstances in which it interferes with making informed decisions.

Respect for the autonomy of individuals, in the process of obtaining informed consent, means recognition and appreciation of their specific capacities and Informed Consent for Schizophrenic Patients perspectives. This means that individuals should not be interfered with when making medical decisions, thus enabling them to act as they choose. Respect for autonomy involves the acknowledgement of another's right to their own decisions, whereas disrespect for autonomy "involves attitudes and actions that ignore, insult, or demean others". This implies, from an ethical point of view, that we should respect not only actions we consider to be correct, but also actions with which we may not agree.

On the basis of this argument, it cannot be claimed that all individual's suffering schizophrenia are incapable of giving informed consent. This capability varies with individuals and over time. Some patients will still retain the capacity to make decisions while others will not. It is vital in schizophrenia treatment to recognise that patients are heterogeneous and vary so greatly in personality, values and ideals.

Mental illness carries a very important stigma and there is often "a presumption of an association between mental illness and impairment of autonomy" and in many ways these two reasons are related.

The average time to remission under treatment is about 3 months. When time required to obtain remission is greater than the degree of remission is lower. Cognitive performance is considered to be the most important factor contributing to the recovery in functional [116]. Examination of longitudinal short-term patients in first episode of schizophrenia, demonstrates a pattern of neuropsychological deficits remarkably constant over time [117]. Recent studies highlight the correlation between the duration of untreated psychosis and cognitive deficits in patients with a first episode of schizophrenia. The duration of untreated psychosis is greater, the greater the extent of cognitive deficits. It thus appears that the function of the prefrontal cortex begins to deteriorate from the beginning of psychosis and it is obvious for those with a longer duration of untreated psychosis [118]. Moreover, some studies have found an association between the tracking duration of untreated psychosis and poor prognosis as evidenced by the rate of relapse and the remission achieved [119].

Stigma

The stigma attributed to this disorder, which are present worldwide, can also be so powerful for family and for individuals and may determined delay of treatment.

Despite recently programs for public education campaigns, there is a view that schizophrenia has poor prognoses and this may induced a negative or denial view. This could result in demoralisation or even depression in patient's family.

Some authors have also suggested that the stigma that lies on mental illness in many societies may cause denial of their symptoms in order to keep the social status and social relationships. Such an individual may reject a medical explanation, not because of a lack of conscience, but because he gives priority to maintaining relations and social position which otherwise he would be loosed.

The length of time between the onset of psychotic symptoms and initiation of therapy (also known as the duration of untreated psychosis) is found to be variable depending on: ethnic and cultural heritage, the degree of community tolerance, the level of stigma, and the levels of psychopathology.

The length of psychosis before treatment was found to be particularly traumatic for patients and their families with high rates of self-harm, suicide or suicidal intentions, family distress, interference of the police, forensic acts, drug use, and threatening behaviour perturbing [120].

Confidentiality

Confidentiality is an important tool for protecting the population from discrimination and other forms of stigma. The challenge of obtaining consent is closely related to problems of patient privacy and confidentiality. Some ethicists explain that our notions of confidentiality

have traditionally been built on the ‘personal account’ model, in which health information belongs to that patient alone.

The setting for treatment determines confidentiality. If it is attempted through general hospitals, it is difficult to be kept confidential because the patient may be evaluated by many physicians in order to eliminate other possible diagnostics. Full confidentiality is more easily preserved if treatment process is performed in specialized clinics or through other medical services (private practice).

The concept of confidentiality therefore may extend beyond secure medical records. It may include not only what is told and to whom, but in the same time what type of language is used and what kind of messages are implied.

The decision "*to treat*" must have an ethical significance to justify the intervention. The current laws, justifies involuntary internment and treatment through the Law on Mental Health and Protection of Persons with psychiatric disorders. Involuntary treatment is justified on the basis of lack of insight and must be judged very carefully. The risk of disability justifies involuntary treatment even it is a significant reduction of freedom as it is written in ethical concepts. The absence of the conscience of the disease is a cognitive disability justifying the intervention in those circumstances in which it

interferes with making best and appropriate decisions for mental health. All this leads to conclusion that delaying treatment causes further problems in development of individuals with schizophrenia regarding social and professional functioning. Possible minimizing the time elapsed from the onset of symptoms and initiation of therapy remains a major goal in schizophrenia.

Ethical guidelines for the research and implementation of treatment are necessary and should be followed by psychiatrists, general practitioners and families in order to ensure the right and optimal access in early stages of schizophrenia.

2. Psychiatric emergencies-focus on clozapine

2.1 Clozapine world wide differences

Nielsen J, Young C, Ifteni P, Kishimoto T, Xiang YT, Schulte PF, Correll CU, Taylor D. Worldwide Differences in Regulations of Clozapine Use. CNS Drugs. 2016 Feb;30(2):149-61.

Clozapine remains the drug of choice for treatment-resistant schizophrenia. As a consequence of its long history and complex pharmacology, we suspected wide variation in the regulations of clozapine useacross different countries. Summary of product characteristics from clozapine manufacturers,and local and national guidelines in the following selected countries were reviewed: China, Denmark, Ireland, Japan, Netherlands, New Zealand, Romania, United Kingdom and USA. Clozapine isavailable as tablets in all countries, as an oral suspension in all included countries except for Japan and Romania, as orally disintegrating tablets in the USA and Chinaand as an injectable in the Netherlands. General practitioner prescribing isonly available in the Netherlands, New Zealand, UK and USA. Although, with some restrictions in some of the countries. In Ireland and China, clozapine isonly dispensed through hospital pharmacies. Hematological monitoring ismandatory in all countries, but varies substantially in frequency, e.g.,in Denmark hematologic monitoring is mandatory weekly for 18 weeks, followed by monthly monitoring, compared to Japan where blood work is requiredweekly for 26 weeks, followed by bi-weekly hematologic monitoring thereafter. In mostincluded countries, except for Denmark, Romania and the Netherlands, the manufacturer provides a mandatory hematological monitoring database, and dispensing of clozapine isnot permissible without acceptable white blood count and absolute neutrophil countresults. Local guidelines in New Zealand recommend echocardiography and routine troponin during the initial phases of treatment with clozapine. Regulations of clozapine vary widelyas regards to rules of prescribing and monitoring. A world-wide update and harmonization of these regulations isrecommended.

In 1959, the molecule clozapine was identified by the pharmaceutical company Wander Laboratories. However, clozapine was not introduced into the market until the first part of the 1970s [121].Clozapine was the first atypical antipsychotic has a low propensity to cause extra-pyramidal side-effects (EPS). In 1975, clozapine was withdrawn because of eight fatal cases of clozapine induced agranulocytosis in Finland, an adverse effect not observed in the initial studies [122]. Despite clozapine only being available for a short period of time, it had

improved the symptoms of many patients based on clinical observation, which ultimately led to its re-introduction. This in turn provoked the development of mandatory hematological monitoring, which hasalmost eliminated the risk of fatal agranulocytosis [123]. Clozapine was not introduced in the US until 1990 after the pivotal study by Kane et al proved that clozapine was significantly superior to chlorpromazine in patients with schizophrenia resistant to retrospective antipsychotic treatment and one prospective antipsychotic trial [124].

Clozapine is a complex antipsychoticwith binding affinities for a wide variety of receptors and pharmacologically active metabolites [125, 126]. The unique mechanism of clozapine that confers superior antipsychotic efficacy is far from fully elucidated. Clozapine possesses only minor affinity for the D2 receptor but relatively higher affinity for both the D1 and the D4 dopamine receptor [127]. Additionally, clozapine has high affinity for the 5-HT2A receptor and partial agonistic action at the 5-HT1A receptor, which likely also contributes to the low risk of EPS [128, 129].

Clozapine also has strong binding affinities for muscarinic receptors, and its metabolite, desmethyl-clozapine, shows partial and full agonist activity on some of the muscarinic receptor subtypes , which may contribute to the unique mechanism of clozapin. In addition, clozapine possesses immunomodulatory properties, which may also be involved in the unique effects of clozapine [130]. Furthermore, clozapine is an agonist at the NMDA receptor glycine site and improves glutamatergic homeostasis in different ways [131].

The superiority of clozapine for treatment resistant schizophrenia has been documented in several clinical trials [132]. Despite non-response to other antipsychotic drugs, the chance of responding to clozapine is more than 60% [133]. The use of clozapine is cost-efficient because of reduction in hospitalizations [134,135]. Despite these advantages, the use of clozapine in patients with schizophrenia varies substantially world-wide with rates as high as 60% in some parts of China to as low as 2-3 % in some parts of the USA [136].

In addition to the effects in treatment resistant schizophrenia, clozapine has also shown benefits in a wide variety of serious psychiatric conditions. Clozapine shows anti-suicidal and anti-aggressive properties in patients with schizophrenia and seems to reduce hospitalizations and bed days as well as intentional self-harm in bipolar patients. Additionally, clozapine has shown benefits for tardive dyskinesia and psychosis in patients with Parkinson’s disease.

In addition, to the risk of agranulocytosis, myocarditis, gastro-intestinal hypomotility/ileus, seizures, substantial weight gain and sedation, and it is for these reasons not considered as a

first line antipsychotic. Most treatment guidelines recommend clozapine after inadequate response to at least two antipsychotics.

As clozapine has a crucial role in the treatment of several serious psychiatric disorders having also a long controversial history, we decided to describe and discuss the differences in the world wide regulations of clozapine use.

The following authors were responsible for providing data from their respective countries, Christoph Correll (USA), Petru Ifteni (Romania), Taishiro Kishimoto (Japan), Jimmi Nielsen (Denmark), Peter Schulte (Netherlands), David Taylor (Ireland and United Kingdom (UK)), Yu-Tao Xiang (China) and Corina Young (New Zealand). As the aim of this review was to describe the diversities of clozapine prescribing and monitoring countries were selected based on known diversities and per se are not necessarily representative for all countries around the world.

The authors reviewed the summary of product characteristics (SPC) from all manufacturers providing clozapine to the market as of January 31, 2015. In addition, we reviewed information from national guidelines about clozapine in those same countries as listed above.We divided our assessment into the following groups: available brands/generics and product information, prescribing practice, hematological monitoring and other monitoring, recording both mandatory and non-mandatory, but "recommended" practices.

The number of different brands available in each country variesbetween one to eightas shown in table 1. Orally disintegrating tablets were only available in the USA and China, but oral suspension was available in China, Denmark, Ireland, the Netherlands, New Zealand, UK and the USA. Injectable clozapineis only available in the Netherlands as an unlicensed medicinal product by a hospital pharmacy (Clozapine injection 125 mg = 5 ml, supplier Brocacef Ziekenhuisfarmacie). The maximum licensed dosage is 900 mg/day in all countries, except for Japan where it isonly 600 mg. In addition, the Dutch clozapine guideline states that higher dosage is useful if the plasma level threshold of 400 ng/ml is not reached otherwise, and that combination with fluvoxamine may be used if the patient refuses to ingest numerous tablets.

Clozapine is licensed in all countries for treatment resistant schizophrenia (TRS) according to the SPC. The criteria for treatment resistant schizophrenia varies among the included countries. In the USA, TRS is defined as "Only severely ill patients not responding to standard antipsychotic treatment", whereas in most other countries it isdefined as inadequate response to at least two antipsychotics, at least one of them having tobe a second generation antipsychotics (SGA). Minimum duration of treatment or dosage is not otherwise specified.

Clozapine is licensed for treatment of psychosis in Parkinson's disease patients in most countries, except for China, Japan, USA and New Zealand, whereas clozapine is only licensed for suicidal behaviors in patients with schizophrenia in the USA and Romania.

The national and local guidelines of many countries recommendclozapine for more indications than the SPC. For example, the Chinese Medical Association recommends clozapine in addition to the above mentioned indication also for patients with schizoaffective disorder, treatment resistant mania or severe treatment resistant psychotic depression and for other treatment resistant psychiatric disorders: patients with pervasive developmental disorder, autism or obsessive-compulsive disorder.

The Dutch Clozapine Guideline also recommends clozapine for treatment resistant schizoaffective disorder, bipolar disorder and depressive disorder with psychotic features; treatment resistant substance abuse or dependence in patients with schizophrenia or schizoaffective disorder; treatment resistant aggression in schizophrenia or schizoaffective disorder and in exceptional cases: treatment resistant aggression and/or self-mutilation in borderline personality disorder, autism or severe intellectual disability.

Prescribing practice

An overview of the prescribing practice is shown in table 2. Most countries have a national guideline for prescribing antipsychotics, which includes information on clozapine. In Japan, psychiatrists and pharmacists have to undergo a 2-3 hour e-learning program before they are allowed to prescribe and dispense clozapine.

General practitioner (GP) prescribing is only possible in the Netherlands, UK, USA and New Zealandand in the UK and New Zealand only as a shared care project, and excludes patients with unstable blood counts or mental state.

Dispensing of clozapine is in some countries only allowed by hospitals. In Ireland, one manufacturer's productis allowed to be dispensed from community pharmacies, whereas the other manufacturer's product is only allowed to be dispensed from hospital pharmacies. In some countries with company-operated blood monitoring databases, such as in the UK and New Zealand, the community pharmacies have to register with a clozapine blood monitoring system in the same way as hospital pharmacies.

In Japan clozapine could only be initiated during in-patient stay, this was not true in any of the other included countries. In all included countries, clozapine should be titrated again in case of having been discontinued for more than 2 days.

Hematological monitoring

Except for China, Denmark, Romania and the Netherlands, all the included countries have a database for hematological monitoring run by the manufacturer.

The mandatory hematological monitoring regimen varied from country to country. Both white blood cell (WBC) and absolute neutrophil count (ANC) monitoring are mandatory in all countries. In Denmark, the Netherlands and New Zealand, the monitoring frequency is weekly for 18 weeks and then monthly, whereas in Ireland and the UK it was weekly for 18 weeks, then bi-weekly from 19-52 weeks and then monthly. In the USA, the weekly monitoring ismandatory the first 26 weeks followed by bi-weekly blood testsfor the next 26 weeks and then monthly. The system is similar in Japan, except that bi-weekly blood monitoring has to be continued and is not replaced by monthly blood sampling.

Monitoring thrombocytes is only mandatory in the UK according to the SPC of Zaponex,whereas the SPC in most other countries specifies only that discontinuation should occur when thrombocytes are <50,000/mm^3.

New Zealand and UK accepts lower ANC and WBC values during long-term treatment(WBC $\geq 2.5x10^9$ and ANC$\geq$ $1.0x10^9$) compared tonew and interrupted patients (WBC $\geq 3.0x10^9$ and ANC$\geq$ $1.5x10^9$). UK also accepts lower limits for patients with benign ethnic neutropenia (WBC $\geq 3.0x10^9$ and ANC$\geq$ $1.5x10^9$). For these patients a written approval from a hematologist is warranted before clozapine can be initiated.

Resuming hematological monitoring of clozapine also differed between the included countries. In the SPC from the USA, monitoring could be reduced to weekly for six weeks when patients had previously been treated for more than 12 months and the discontinuation gap was less than one month. The SPC from other countries, such as New Zealand, Netherlands and Denmark state that if patients had been treated with clozapine for more than 18 weeks and the gap was between 3 days and 4 weeks, hematological monitoring should occur weekly for an additional 6 weeks before returning to monthly monitoring. If the discontinuation gap exceeded 4 weeks, new weekly monitoring for 18 weeks is required.

Other types of monitoring

ECG monitoring isnot mandatory according to the SPC in any of the included countries, but referral to a specialist, which could include an ECG, was recommended in case of abnormal cardiac findings during physical examination or in those with a history of cardiac illness. However, in Denmark the national guideline, and in New Zealand a local guideline state that ECG monitoring is mandatory.

Referral for echocardiography is only mandatory according to a local guideline in New Zealand. Weekly troponin and C-reactive protein monitoring during the first month of clozapine therapy are also mandatory according to this same guideline.

Blood pressure monitoring is only mandatory for patients with Parkinson's disease according to the SPC, but recommended or mandatory in most local and national guidelines, such as those by the National Institute of Clinical Excellence (NICE), which recommends blood pressure monitoring at 12 weeks, at 1 year and then annually for all antipsychotics.

Monitoring for constipation is not included in the SPC of any of the included countries, but are recommended in some guidelines, e.g., the Dutch guideline where it is recommended to ask the patient regularly (weekly) about any constipation during clozapine initiation and to start immediately a laxative in cases that constipation is confirmed.

No SPC recommended monitoring of clozapine plasma levels, but it is recommended in some of the national guidelines.

The major finding of this review is the substantial variation across the selected 9 countries on 4 continents in the regulations and recommendations regarding clozapine. Several brands are available in most countries except for Japan, where Novartis is the only provider. The reason for this may be the late introduction of clozapine in Japan (2009). In the USA, an oral disintegrating tablet is available and an oral suspension is available in Denmark, Ireland, the Netherlands, New Zealand, UK and USA. Injectable clozapine for intramuscular use is only available in the Netherlands.

Clozapine is licensed up to 900 mg/day in most countries but only up to 600 mg/day in Japan. Although it is poorly investigated, Asian patients may have a slower metabolism andmay warrant lower dosages [137]. In general, psychiatrists are reluctant to use clozapine above 600 mg/day [138]. Clozapine provokes large inter-individual variation in pharmacokinetic properties and although response occurs across the whole range of plasma levels,the chance of response is twice as high above a clozapine plasma level of around 400 ng/ml. Therefore, some patients may even warrant higher dosages than 900 mg because of ultra-high activity in the CYP1A2 enzyme [139]. Therapeutic drug monitoring (TDM) is not mandatory in any country,althoughit may be of important value in the optimization of clozapine treatment. It is worth noting that a large number of patients respond at much lower concentration than suggested above and clozapine should always be used at the lowest effective dose in order to minimize the burden of adverse effect.

Clozapine is licensed for treatment resistant schizophrenia in all countries. However, the definition for treatment resistant schizophrenia varies considerably between countries. In the

USA, treatment resistance is defined as not responding adequately to standard antipsychotic treatment, whereas in Denmark, the Netherlands, Ireland, New Zealand, Romania, Japan and UK treatment resistance is specified as suboptimal response to at least two antipsychotics (at least one atypical antipsychotic). This recommendation is in line with most treatment guidelines that suggest that clozapine should be offered after inadequate response to two antipsychotic drugs. However, several studies have documented a substantial delay in the prescribing of clozapine compared to the treatment guidelines. This delay may reduce the chances of response and negatively affect the outcome of the disease. Earlier clozapine prescription may be achieved by regular audits, establishing specialized outpatient teamswith the focus to increase the prescription rate of clozapine or implementing procedures that facilitate clozapine prescribing, such as using point-of-care devices for hematological clozapine monitoring.

Clozapine is licensed only in the USA and Romania for reducing suicidal behavior in patients with schizophrenia and schizoaffective disorder, despite extensive documented benefits for suicidality in this population. In contrast, clozapine is only licensed in Europe for Parkinson's disease-related psychosis. Clozapine remains recommended for this indication.The guidelines in most countries recommend clozapine for more indications than the SPC, such as treatment resistant bipolar disorder where clozapine is only used negligibly [19]. More should be done to inform psychiatrists of the other potential indicationsin which patients remain treatment resistant despite multiple first-line approaches and clozapine use could be beneficial.

The mandatory monitoring system varied substantially between countries. Japan seems to have the strictest monitoring regulations with bi-weekly blood tests as the longest allowed interval. In contrast, Denmark, New Zealand, Romania and the Netherlands allowed monthly blood samples after 18 weeks of treatment. Except for Ashkenazi Jews, which have a higher risk of agranulocytosis, the variation in blood sampling frequency is not justified by variation in risk of agranulocytosis. We did not find any studies investigating the effects of the different monitoring frequency.

In some countries, the clozapine manufacturers are obliged to provide a national monitoring database to ensure that patients with a history of agranulocytosis are not re-exposed to clozapine and clozapine is not continued in case of very low WBC or ANC. In these countries, documentation for "green values" of WBCANC should be provided to the pharmacy before dispensing can occur. This may refer to the "no blood – no drug principle". In other countries, e.g., Denmark, clozapine can be prescribed without registration in any

register and with no restrictions regarding the amount of clozapine that can be picked up from the pharmacy at the same time. Additionally, the pharmacy has no role in double-checking whether the patients comply with the hematological monitoring. Although it seems reasonable for safety reasons to have a hematological database, it may also increase the complexity of clozapine prescribing and preclude some psychiatrists from prescribing clozapine. Unfortunately, we arenot able to identify any studies evaluating the different systems as regards to safety or influence on prescription rates. This call for large comparison studies in order identify the most appropriate monitoring system and blood sampling frequency, both as regards to safety, compliance and cost-effectiveness. In the future, genetic testing may reduce the frequency or need for routine hematological monitoring.

Only SPC from UK covers differentiated limits for patients with benign ethnic neutropenia. As this is most likely a challenge in other countries, other guidelines and SPC should adapt these differentiated reference values in order to make it feasible to treat this group of patients with clozapine properly. Currently, the US Food and Drug Administration (FDA) implement the shared risk evaluation and mitigation strategy program called Clozapine REMS. This program includes a centralized register replacing the registers from the manufacturers and ANC but not WBC should be monitored. Additionally new values for patients with BEN are introduced in the US as well.

Clozapine may cause several cardiac adverse effects, such as myocarditis, cardiomyopathy, sinus tachycardia and T-wave alterations, but despite this ECG monitoringis not mandatory according to any SPC. As ECG is a cheap, non-invasive examination and potentially helpful for diagnosing these cardiac adverse effects, routine ECG monitoring may be worth considering. Routinely monitoring of troponin has been suggested too for diagnosing myocarditis, but troponin monitoring was only mandatory during first weeks of treatment according to one local guideline in New Zealand.

However, implementation of expanded monitoring guidelines should be weighed cautiously, as this increase burden of monitoring may prevent psychiatrists even more from prescribing clozapine. In addition, neither troponin levels nor ECG are specific markers of clozapine's cardiac adverse effects, and false positive findings may occur, deterring further from clozapine use. Although the rate of clozapine associated myocarditis is debatable, with likely some under diagnosing, the mortality due to myocarditis seems to be as low as 0.02% with no evidence of benefits or risks of screening. Meanwhile, clinicians should be aware of the signs and symptoms of myocarditis, which occur most often during the first month of treatment and screen for tachycardia, exertional dyspnoea, chest pain, arrhythmia, fever, fatigue and

dizziness. If these occur, measurement of troponin and an ECG should be obtained. Interestingly, SPCs do not specify recommendations about monitoring for gastro-intestinal hypomotility, despite the fact that mortality from ileus is four to ten times higher than from agranulocytosis. Clozapine induced constipation is a frequent side effect of clozapine, which causes distress and may lead to ileus and death in 0.1% of clozapine users. Therefore, screening and treatment should be implemented as recommended in the Dutch guideline.

Clozapine regulations varies around the world, both as regards to indications and monitoring. National and local guidelines included more indications and psychiatrists should be aware that clozapine may be used for other indications than specified in the SPC, which generally includes treatment resistant schizophrenia only. The SPC describes strict hematological monitoring, but no recommendations about monitoring for constipation/ileus or myocarditis, which may also lead to a fatal outcome. A harmonization of SPCs and national guidelines based on the current evidence level is recommended, and more should be done to implement appropriate clozapine treatment and to prevent complications and delay of a potentially lifesaving treatment.

2.2 Clozapine for treatment refractory Bipolar Disorder

***Ifteni P**, Correll CU, Nielsen J, Burtea V, Kane JM, Manu P. Rapid clozapine titration in treatment-refractory bipolar disorder. J Affect Disord. 2014 Sep;166:168-72*

Clozapine has been used in bipolar disorder refractory to other therapeutic modalities in the United States since 1989 [140]. Its use has been shown to reduce symptom severity in patients with manic and mixed-state episodes, decrease the need for psychotropic co-medications, and reduce the number of psychiatric hospitalizations [141]. Clozapine has been effective in acute mania without psychotic features and is therefore considered to have mood-stabilizing properties. The average clozapine dose effective in bipolar disorder is substantially lower than the daily amount required for symptom control in patients with schizophrenia [142] and serious adverse drug reactions, such as agranulocytosis and seizures, have been very rare.

Treatment with clozapine is usually initiated in hospital settings, and clinical guidelines and manufacturers' recommendations suggest starting with 12.5–25 mg/day and to gradually increase the dose by 25 mg steps in week 1 and 25–50 mg steps thereafter over a two-to-three week period until reaching the target dose. This recommendation has not been derived from rigorous controlled trials, but rather from reports of hypotension observed during the initial clinical testing of clozapine and case-series correlating the occurrence of seizures with high clozapine dosages. The long clozapine titration period may delay the adequate control of symptoms and could prolong the hospital stay at great emotional distress for patients and clinical staff involved in their care.

Health care utilization and costs incurred for the treatment of bipolar patients are four times greater compared with age and gender-matched individuals. Inpatient care accounts for the largest proportions of medical expenditures for adults with bipolar disorder in the United States. An analysis of the societal cost of bipolar disorder in Sweden indicated that the monies spent on inpatient care exceed the combined cost of outpatient care, pharmaceuticals and community support services [143]. From this vantage point, we believe that the long titration period may discourage the use of clozapine in a resource-tight, cost-conscious environment.

In our recent study, we have shown that rapid clozapine titration was effective and safe in patients with schizophrenia. Symptom control was obtained with an average dose of 372 ± 181 mg/day after 5.1 ± 4.0 days in 111 patients with treatment-refractory schizophrenia and none had seizures, severe hypotension, myocarditis or other major adverse effects. In the current study, we compare the hospital outcome of patients with treatment-refractory bipolar disorder who received clozapine according to a rapid or standard clozapine titration protocol used as part of clinical care on two different inpatient units of the same hospital. Based on our findings in schizophrenia patients, we hypothesized that the methods are equally effective and safe, but that patients treated with the rapid titration method will require fewer days until they are ready for discharge.

The patients described in this report were admitted to a 120-bed, free-standing psychiatric teaching hospital located in Brasov, Romania. The hospital has two 60-bed units, each with their own permanent clinical staff organized as self-standing teams. Patients referred for hospitalization are admitted, on alternate days, to one of the two units. The clinical care is coordinated by board-certified psychiatrists affiliated with the local medical school.

From January 1, 2005 through December 31, 2013, the hospital admitted 931 adult patients diagnosed with bipolar disorder according to DSM-IV-TR criteria. Within this cohort, 67 individuals (7.2%) required treatment with clozapine. Consent for treatment was obtained in accordance with the procedures stipulated by the hospital's Ethics Committee. The retrospective chart review was approved by the hospital's Ethics in Research Committee.

Patients with manic or mixed episodes, with or without psychotic features, were considered refractory to treatment if their symptoms did not improve after two or more trials of antipsychotic drugs, administered in conjunction with first line mood- stabilizing agents. Patients switched to clozapine received the drug in combination with valproate or as monotherapy

On one of the units, clozapine was initiated with a dose of 25 mg in the first day of treatment, followed by daily upward adjustments of 25–50 mg (i.e., standard titration). On the other unit, oral administration of clozapine was started with a dose of 25 mg, followed by additional doses of 25–50 mg administered as needed every 6 h in the first 24 h, up to a maximum of 100 mg.

On subsequent days, the dose was increased by 25–100 mg (i.e., rapid titration). The titration was continued until satisfactory symptom control or development of major side effects. Each titration method was used as a matter of routine and both had been approved without restrictions by the hospital's Ethics Committee for all diagnoses requiring the use of clozapine.

Blood pressure, heart rate and temperature were recorded daily. A complete blood count, metabolic panel and an electro-cardiogram were obtained on admission. Complete blood counts were checked weekly throughout the hospital stay. The severity of illness was ascertained with the Clinical Global Impression Scale (CGI) on admission, at the start of clozapine treatment, and on the day of actual discharge from the inpatient unit. The psychiatrists' daily progress notes were used to determine the day each patient was considered ready for discharge. Adverse drug effects were assessed daily throughout the hospital stay.

Demographic, clinical and clozapine-related characteristics of patients treated with the standard and rapid clozapine titration protocols were compared using analysis of variance. In an intent- to-treat analysis, the primary outcome was the time interval, in days, from the first dose of clozapine until readiness for discharge. Secondary outcomes included total length of stay and CGI-Severity score at time at time of discharge.

The groups of patients treated with clozapine according to the rapid (N = 41) and standard (N = 26) titration methods were similar with regard to age, gender, frequency of manic and mixed episodes, presence of psychotic features, age at onset and duration of bipolar disorder, smoking status, body mass index and severity of illness at the time of admission.

Table 1
Demographic features and psychiatric characteristics.

Characteristic	Total ($N=67$)	Rapid clozapine titration ($N=44$)	Standard clozapine titration ($N=23$)	*p-Value*
Age, years ± S.D.	**39.6 ± 13.0**	**41.3 ± 12.7**	**36.3 ± 13.0**	**0.14**
Male gender, *N* (%)	**37 (55.2%)**	**27 (61.4%)**	**10 (43.5%)**	**0.16**
Smoking, *N* (%)	**43 (64.2%)**	**28(63.6%)**	**15 (65.2%)**	**0.88**
Body mass index, (kg/m^2 ± S.D.)	**25.3 ± 3.1**	**25.3 ± 3.4**	**25.4 ± 2.7**	**0.97**
Bipolar disorder subtype				
Manic episode	**46 (68.7%)**	**30 (68.2%)**	**16 (69.6%)**	**0.91**
Mixed episode	**21 (31.3%)**	**14 (31.8%)**	**7 (30.4%)**	**0.91**
Psychotic features	**25 (37.3%)**	**13 (29.6%)**	**12 (52.2%)**	**0.07**
Age of onset, years ± S.D.	**28.0.0 ± 9.0**	**29.3 ± 9.8**	**25.5 ± 7.0**	**0.10**
Substance use disorder				
Alcohol	**27 (40.3%)**	**17 (38.6%)**	**10 (43.5%)**	**0.70**
Drugs	**5 (7.5%)**	**2 (4.6%)**	**3 (13.0%)**	**0.22**
Duration of illness, years ± S.D.	**11.6 ± 9.8**	**12.0 ± 9.0**	**10.8 ± 11.1**	**0.64**
CGI$_s$ at baseline, score ± S.D.	**6.0 ± 0.6**	**6.0 ± 0.7**	**6.0 ± 0.4**	**0.99**

CGI$_s$: Clinical Global Impression, severity.

Twenty-five patients had at least two unsuccessful antipsychotic trials prior to admission and were started on clozapine on the first hospital day. The proportion of these patients who were diagnosed as treatment-refractory on admission was greater among those admitted to the unit using the rapid clozapine titration method (52.3% vs. 13.0%, p<0.002). The number of antipsychotic trials prior to clozapine initiation during the index hospitalization (range: 0–4) was not significantly different between groups. The choice and maximum dosage of antipsychotics before starting clozapine were also similar in the two groups (Table 2).

Table 2
Psychotropic treatment prior to starting clozapine.

Characteristic	Total (*N*=67)	Rapid clozapine titration (*N*=44)	Standard clozapine titration (*N*=23)	*p-Value*
Patients receiving antipsychotic trials during hospitalization prior to starting clozapine	**41 (61.2%)**	**21 (47.7%)**	**20 (87.0%)**	**0.002**
Haloperidol				
Number of patients	23 (34.3%)	12 (27.3%)	11 (47.8%)	0.10
Maximum dose, mg ± S.D	9.6 ± 3.8	10.6 ± 4.5	8.4 ± 2.8	0.18
Olanzapine				
Number of patients	18 (26.9%)	9 (20.5%)	9 (39.1%)	0.11
Maximum dose, mg ± S.D	18.9 ± 3.3	18.9 ± 3.3	18.9 ± 3.3	1.0
Levopromazine				
Number of patients	12 (17/9%)	8 (18.2%)	4 (17.4%)	0.94
Maximum dose, mg ± S.D	106.3 ± 78.9	93.8 ± 58.7	131.2 ± 114.3	0.45
Quetiapine				
Number of patients	11(16.4%)	7 (15.9%)	4 (17.4%)	0.88
Maximum dose, mg ± S.D	627.3 ± 163.4	614.3 ± 146. 4	650.0 ± 191.5	0.73
Amisulpride				
Number of patients	4 (6.0%)	1 (2.3%)	3 (13.0%)	0.09
Maximum dose, mg ± S.D	575.0 ± 173.2	800.0 ± 0.0	500.0 ± 173.2	0.27
Aripiprazole				
Number of patients	3 (4.5%)	2 (4.6%)	1 (4.4%)	0.97
Maximum dose, mg ± S.D	16.7 ± 0.0	20.0 ± 0.0	10 ± 0.0	
Inpatient Antipsychotic Trials Prior to Starting Clozapine	**1.1 ± 1.0**	**0.8 ± 1.1**	**1.4 ± 08**	**0.06**
Valproate use				
Number of patients	57 (85.1%)	36 (81.8%)	21 (91.3%)	0.28
Maximum dose, mg ± S.D	1121.1 ± 403.4	1090.3 ± 4242.7	1173.8 ± 365.9	0.45

In the rapid titration group, the average maximum dose of clozapine was 361 mg/day, which was reached already after 4.4 days. In the standard titration group, the average maximum dose of clozapine was 387 mg/day, which was achieved after 12.4 days (Table 3).

Table 3
Clozapine titration time, dose and effect.

Characteristic	Total (*N*=67)	Rapid clozapine titration (*N*=44)	Standard clozapine titration (*N*=23)	*p-Value*
Days in hospital until clozapine initiation ± S.D.	**7.7 ± 8.1**	**6.7 ± 8.4**	**9.3 ± 7.5**	**0.19**
Titration days ± S.D.	**7.1 ± 1.2**	**4.4 ± 1.0**	**12.4 ± 1.6**	**< 0.001**
First day dose, mg ± S.D.	**64.2 ± 21.3**	**84.1 ± 25.9**	**26.1 ± 5.2**	**< 0.001**
Maximum dose, mg ± S.D.	**369.8 ± 118.5**	**360.8 ± 108.7**	**387.0 ± 135.9**	**0.39**
CGI-S when clozapine started ± S.D.	**5.9 ± 0.4**	**5.9 ± 0.5**	**6.0 ± 0.3**	**0.41**
Days in hospital between clozapine initiation and readiness for discharge ± S.E.	**14.2 ± 0.6**	**12.9 ± 0.9**	**15.8 ± 1.0**	**0.038**
CGI-S at time of discharge ± S.D.	**3.1 ± 0.3**	**3.1 ± 0.4**	**3.1 ± 0.3**	**0.96**

CGI-S: Clinical Global Impression Scale-Severity.

The severity of symptoms at the start of clozapine treatment and the magnitude of change at the time of discharge were similar in the two groups (Table 3). The utilization of valproate was similar in the 2 groups (Table 2). The proportion of patients requiring benzodiazepines after clozapine initiation was smaller in the rapid titration group (87.0% vs. 63.6%, $p < 0.044$).

The overall length of stay was 26.3 ± 10.8 days in the rapid titration group and 33.3 ± 10.4 days in the remaining clozapine- treated patients ($p < 0.013$). The number of days from starting clozapine until readiness for discharge (12.7 ± 6.3 vs. 16.5 ± 5.8) was significantly shorter in the rapid titration group after adjust- ing for the proportion of patients with psychotic features and the number of inpatient antipsychotic trials and psychotropic co- medications ($p < 0.0077$).

Clozapine was discontinued in 5 (7.5%) patients. One patient developed excessive sedation during standard titration. In the rapid titration group, one patient's family withdrew consent for treatment, one developed asymptomatic hypotension (lowest arterial blood pressure 90/60 mmHg), one had pneumonia and was transferred to a general hospital, and one experienced excessive sedation. None of the patients developed neutropenia, symptoms suggestive of myocarditis, neuroleptic malignant syndrome or drug-induced movement disorders.

The number of patients suffering a relapse during the 12 months after discharge was similar in the two groups (54.6% vs7.8%, $p < 0.60$).

This retrospective study is the first demonstration of the safety and effectiveness of rapid clozapine titration in treatment-refractory bipolar disorder. The dosage required for the clinically significant improvement in illness severity (approximately 50%), as measured on the Clinical Global Impression Scale, was similar in the rapid and standard titration groups and no major adverse drug reactions were observed. The time interval from the start of clozapine until patients were considered ready for discharge was significantly shorter in the rapid titration group. The 2.9 days difference in favor of the rapid titration was significant adjusting for the presence of psychotic features and number of inpatient antipsychotic trials that marginally differed between the two groups. Taking into account recent Medicare reimbursement

rates [144], the difference translates into a potential saving of $4051/admission.

While the difference of 3.8 days between the two titration schedules may appear small, one needs to bear in mind that even the standard titration schedule used in these clinical setting was faster than the generally utilized and recommended dosing schedule. The general recommendation stipulates daily dose increases of 25 mg on days 3–10 and 50 mg increments per day thereafter, reaching 150 mg at the end of week 1 and 300 mg at the end of week 2 (https://www.clozapineregistry.com/aboutcloza pine/titration.aspx). By contrast, in our study, the standard titration group reached 386 mg/day at 11.5 days, while the rapid titration group reached 370 mg/day at 7.2 days. Thus, benefits of the rapid titration schedule may even be more pronounced compared to the regular (i.e., slower) titration schedule.

The titration rate of lozapine should be tailored to the patient's needs. The initial dose of 12.5 or 25 mg should be considered as a test dose and if this is well tolerated the patients may be eligible for a rapid titration of clozapine. One of the concerns about rapid clozapine titration is the risk of ending up with a higher than necessary dosage and the increased risk of side effects. However, we found no differences in clozapine dose at discharge and no differences in adverse effects necessitating clozapine discontinuation (which was rare) between the two titration schemas. Nevertheless, the benefits of rapid clozapine titration should be balanced against the potential for an increased risk for orthostatic hypotension and seizures. However, this study and our previous work on patients with schizophrenia strongly suggest that rapid titration can safely be administered when warranted.

Although we were not able to detect any difference as regards to side effects or complications between the two titration strategies, a recent study from Australia showed that rapid titration of clozapine was associated with an increased risk of myocarditis.

Our observations add to the evidence of the utility of clozapine in refractory bipolar disorder and support previous work in which clozapine was shown to achieve symptom control more rapidly than chlorpromazine in treatment refractory mania. Nonetheless, a nation-wide Danish study showed that only 1.5% of bipolar patients had been treated with clozapine suggesting substantial

underutilization of this valuable and relatively inexpensive drug. Although studies of clozapine in bipolar disorder are sparse, the drug is recommended for treatment refractory bipolar disorder in the latest version of The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders. The limited data on this indication suggest that some patients not responding to other treatments may respond to clozapine. Additional, high quality randomized controlled studies are warranted to define the exact the role of clozapine in patients with bipolar disorder.

The encouraging results of this study should be interpreted within its limitations. The modest sample size cannot be considered sufficient to detect the occurrence of rare, but potentially very serious adverse side effects, such as agranulocytosis, myocarditis, seizures, venous thromboembolism or neuroleptic malignant syndrome.

The distinction between rapid cycling and non-rapid cycling bipolar patients, a clinical feature possibly related to the response to treatment, could not be analyzed for lack of data.

Finally, the transition to clozapine occurred without a washout period, out of concern for the well-documented worsening of symptomatology during the washout. This approach is consistent with clinical care and was true for both groups, so that biasing the results is less likely to have occurred.

In conclusion, this retrospective study showed that rapid titration of clozapine clozapine with a start dose of 25 mg followed by 25–50 mg administered every 6 h up to a maximum of 100 mg/day during the first 24 h and subsequent increases by 25–100 mg/day thereafter was associated with shorter duration until readiness for discharge compared to "standard" titration. No increase in burden of side effects was found. These encouraging results call for prospective randomized studies of different clozapine titration schemas in a larger sample of patients with bipolar I disorder.

3. Other relevant projects: sudden death in psychiatric patients and in general population.

3.1 Sudden death in dementia

Ifteni P, Grudnikoff E, Koppel J, Kremen N, Correll CU, Kane JM, Manu P. Haloperidol and sudden cardiac death in dementia: autopsy findings in psychiatric inpatients.Int J Geriatr Psychiatry. 2015 Dec;30(12):1224-9

For decades, haloperidol has been the most widely prescribed antipsychotic in oral, intramuscular, or intravenous administration. The US Food and Drug Administration (FDA) has approved haloperidol's use for schizophrenia and Gilles de la Tourette's syndrome, as well as in short-acting injectable formulation for the treatment of severe agitation. The label also allows its use for severely disturbed, non-psychotic, or hyperactive children with accompanying conduct disorders but only after documented failure of psychotherapy or non-antipsychotic medication. Haloperidol is extensively used for the treatment of agitation in medical and psychiatric settings, often in conjunction with a short-acting benzodiazepine. The drug is contraindicated in comatose states of any cause, in patients with Parkinson's disease and toxic central nervous system depression. The use of typical and atypical antipsychotics has been associated with an excess of sudden cardiac deaths in two large epidemiological studies in the United States [145]. Based on death certificates and pharmacy records, these investigations used complex algorithms to adjust for other somatic disorders and concluded that the incidence rate-ratio was more than double in patients prescribed antipsychotic drugs the last month of their life. The findings were hypothesized to be related to the dose-dependent prolongation of myocardial repolarization time, which could lead to torsades de pointes, a potentially fatal ventricular arrhythmia. In 2008, the FDA Center for Drug Evaluation and Research requested a safety labeling change for haloperidol, which highlighted the increased mortality in elderly patients with dementia-related psychosis. The "boxed" warning postulated that these patients were at an increased risk of death while receiving antipsychotic drugs, despite stating also that the "extent to which the findings of increased mortality" in the placebo-controlled trials reviewed by the agency "may be attributed to the antipsychotic drugs as opposed to some characteristic (s) of the patients is not clear" (FDA, 2008). The labeling change for haloperidol represented an extension of a warning, added to its label upon the request of the FDA in 2005, that the use of second-generation antipsychotics nearly doubled the risk of death in elderly patients with behavioral

disturbances. The warning was based on a meta-analysis of 15 placebo-controlled trials (9 unpublished), lasting 10–12weeks in which 3353 patients were randomized to antipsychotics (aripiprazole [three studies], olanzapine [five studies], quetiapine [three studies], risperidone [five studies]) and 1757 to placebo [146]. These analyses indicated that death occurred significantly more often among patients treated with antipsychotics (3.5% vs. 2.3%), resulting in an odds ratio of 1.54 (95% confidence interval [CI]= 1.06–2.23) and a risk difference of 0.01 (95% CI= 0.004–0.02), translating into a number-needed-to harm of 100 (95% CI = 50–250), without indications for significant differences among individual drugs. However, those reports did not evaluate the safety of conventional antipsychotics, and the meta-analyses available at the time were not adequately powered to compare second-generation drugs with haloperidol concerning the risk of iatrogenic death in the elderly with dementia [147]. Using risperidone exposure as the reference, an 80-day study of 33,604 patients with dementia indicated that haloperidol use was associated with a significantly higher mortality rate (relative risk = 1.54, 95% CI = 1.38–1.73), but analyses by cause of death were not performed [148]. These epidemiological reports have major methodological weaknesses with regard to the true frequency and significance of sudden cardiac death in patients treated with haloperidol. First, no anatomical proof was produced to allow the distinction between sudden cardiac deaths and deaths explained by identifiable acute structural pathology.

Sudden cardiac death produced by haloperidol can be assessed only by knowing with precision the cause of unexpected death occurring in hospitals or other settings in which compliance with antipsychotic treatment is verifiable. This level of detail requires complete post-mortem examinations. Such studies are not available probably because autopsies are performed in a small minority (9.5–18%) of patients who die during psychiatric hospitalizations in the developed parts of the world [149]. In this report, we tried to advance the knowledge regarding sudden cardiac death in psychiatric patients by evaluating the findings of a consecutive series of autopsies in psychiatric inpatients with dementia from an Eastern European country where health policies mandate a post-mortem search for the cause of unexpected deaths.

The patients described in this report were admitted to a 120-bed, free-standing, public psychiatric hospital located in Brasov, Romania (population = 277,000). The clinical care is provided by board certified psychiatrists affiliated with the local medical school. Patients deemed by their treating psychiatrist to have a significant medical deterioration are

transferred the same day to the county hospital. The retrospective review of medical records was approved by the hospital's Ethics in Research Committee.

From 1 January 1989 through 31 December 2013, the hospital admitted 1219 patients (724 women and 495 men) with a primary diagnosis of dementia with behavioral disturbance. Antipsychotic drugs were prescribed to 521 (42.7%) patients. Thefirst-generation antipsychotics used were haloperidol (362 patients), levopromazine (34 patients), and chlorpromazine (15 patients), while the second-generation agents included quetiapine (52 patients), olanzapine 30 patients, clozapine (26 patients), and risperidone (2 patients). Death occurred during the hospital stay in 135 patients. At the time of death, 71 (52.3%) patient were treated with antipsychotic drugs. The drugs were haloperidol in 66 (93.0%) patients, quetiapine and olanzapine in 2 patients each, and clozapine in 1 patient.

Definition of sudden cardiac death

Death was sudden in 65 (48.1%) of the 135 patients who died, that is, in 5.3% of the entire dementia cohort. All of these patients died while being asymptomatic or within 1 h of new symptom(s) onset. None of the patients died of physical trauma, homicide, suicide, or accidental drug overdose. As required by countrywide health policy, gross and microscopic post-mortem examinations were carried out within 24 h by board certified pathologists employed by the government in 55 (84.6%) of the 65 patients. Exceptions from autopsy were granted for narrowly defined religious or personal preference reasons in 10 of the cases of sudden death. The diagnosis of sudden cardiac death was made in cases without identifiable acute structural pathology in the heart or other organs [150].

Autopsy findings The 55 patients with dementia (35 men and 20 women) who died suddenly and unexpectedly had a mean age of 79.7 ± 6.5 years and had been under psychiatric care for dementia with behavioral disturbance for 3.1 ± 1.3 years. Vascular and Alzheimer's dementia were diagnosed in 30 (54.6%) and 25 45.5%) patients, respectively. At the time of death, 27 (49.1%) patients were treated with haloperidol at dosages (mean ± SD) of 2.2 mg ± 2.1 mg/day. Thirty (54.6%) patients were receiving benzodiazepines, 6 (10.9%) were on mood stabilizers, and one (1.8%) on an antidepressant. The sudden death occurred on an average of 5.9 ± 3.0 days after admission to the inpatient psychiatric unit. Acute structural pathology sufficient to explain the unexpected death was identified in 37 (67.3%) of the 55 cases. The leading causes of death were myocardial infarction (25.5% of patients), pneumonia (23.6%), and cerebrovascular accidents (10.9%). Other causes of death included myocarditis (3.6%), airway obstruction (1.8%), and upper gastrointestinal bleeding (1.8%). The diagnosis of

sudden cardiac death was made in 18 (32.7%) cases, whose cause of death could not be established at autopsy (Figure 1)

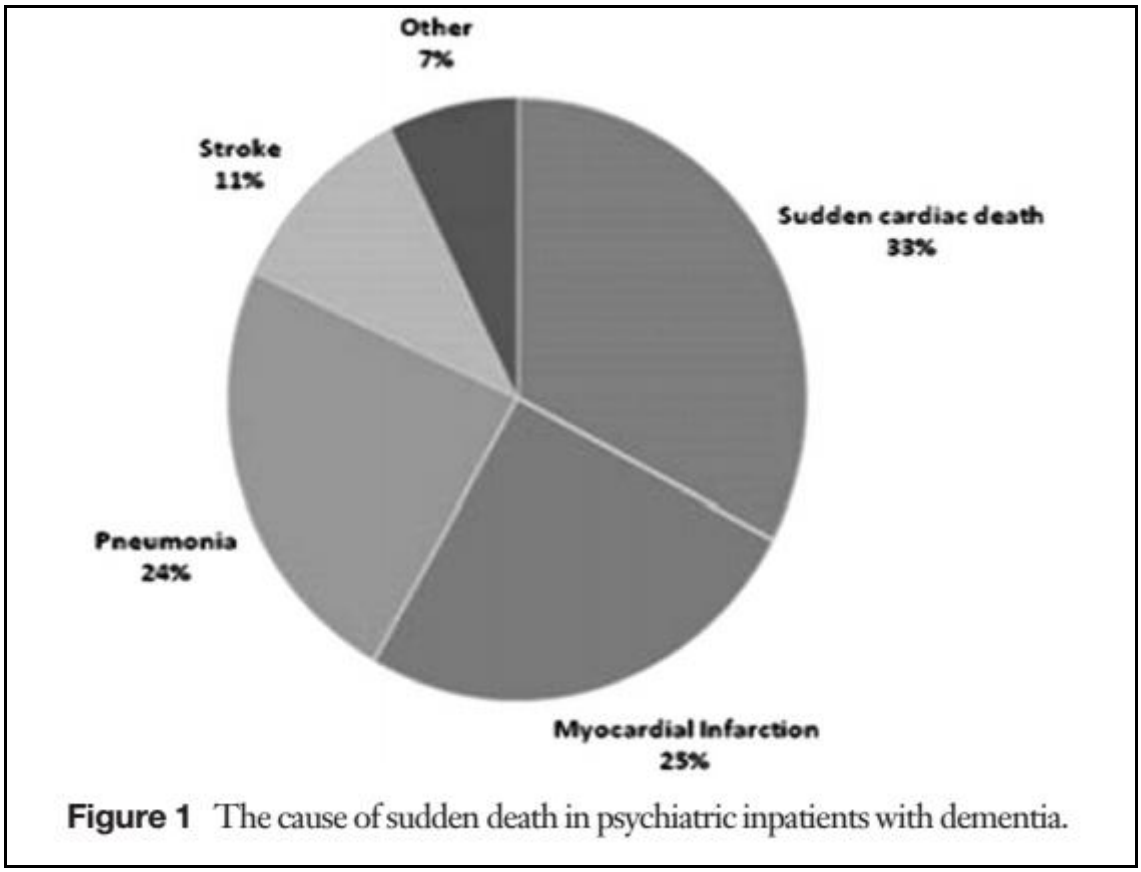

Figure 1 The cause of sudden death in psychiatric inpatients with dementia.

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Patients diagnosed with sudden cardiac death and those with anatomically established cause of death were similar with regard to the use of haloperidol (Table 1). The Sudden cardiac death patients were more likely to suffer from Alzheimer's dementia (Table 1) and to have a past medical history of heart disease (Table 2) than those with acute structural pathology, and less likely to have been treated with a mood stabilizer (Table 1). None of these variables emerged as independent predictors of sudden cardiac death in multivariable backward elimination regression analysis.

Table 1 Demographic and psychiatric features of dementia inpatients who died suddenly

Characteristic	Total ($N = 55$)	Death due to acute structural pathology ($N = 37$)	Sudden cardiac death ($N = 18$)	p
Age, (years ± SD)	79.7 ± 6.5	79.1 ± 6.6	80.8 ± 6.5	0.36
Male gender, *N* (%)	35 (63.6)	26 (70.3)	9 (50)	0.15
Type of dementia, *N* (%)				
Alzheimer	25 (45.5)	13 (35.1)	12 (66.7)	0.027
Vascular	30 (54.6)	24 (64.9)	6 (33.3)	0.027
Psychotic features, *N* (%)	12 (21.8)	7 (18.9)	5 (27.8)	0.46
Duration of dementia-related behavioral disturbance (years ± SD)	3.1 ± 1.3	2.9 ± 1.3	3.6 ± 1.5	0.092
Length of stay (days ± SD)	5.9 ± 3.0	5.9 ± 3.0	5.8 ± 3.0	0.87
Haloperidol use, *N* (%)	27 (49.1)	17 (45.9)	10 (55.6)	0.50
Haloperidol dose at the time of death (mean ± SD/day) and range (mg/day)	2.2 ± 2.1 0.5–9	2.5 ± 2.17 1–9	1.75 ± 2.00 0.5–6	0.382
Psychotropic co-medications at the time of death, *N* (%)				
Benzodiazepine	30 (54.6)	22 (59.5)	8 (44.4)	0.25
Mood stabilizer	6 (10.9)	6 (16.2)	0 (0)	0.024
Antidepressant	1 (1.8)	1 (2.7)	0 (0)	0.37

SD, standard deviation.

Treatment with haloperidol at the time of sudden death The group of 27 patients treated with haloperidol at time of the unexpected death comprised more individuals who had dementia with psychotic features (37.0% vs. 7.1%, p = 0.0095) than the group (N = 28) not receiving antipsychotic drugs.

Table 2 Medical history of psychiatric inpatients with dementia who died unexpectedly

Organ/system involved, *N* (%)	Total ($N = 55$)	Death due to acute structural pathology ($N = 37$)	Sudden cardiac death ($N = 18$)	p
Heart disease	29 (52.7)	15 (40.5)	14 (77.8)	0.0094
Neurological disease	12 (21.8)	9 (24.3)	3 (16.7)	0.51
Kidney disease	8 (14.6)	6 (18.2)	2 (11.1)	0.061
Malignancy	7 (12.7)	4 (10.8)	3 (16.7)	0.55
Diabetes	6 (10.9)	3 (8.1)	3 (16.7)	0.35
Liver disease	1 (1.8)	1 (2.7)	0 (0)	0.37

The groups were similar with regard to age, gender, the etiology and duration of dementia, other psychotropic drugs, and the frequency of diagnoses established at autopsy (Table 3).

Table 3 Cause of sudden death in patients treated with haloperidol

Autopsy findings, *N* (%)	Treated with haloperidol ($N = 27$)	Not treated with haloperidol ($N = 28$)	*P*-value
Acute structural pathology	17 (63.0)	20 (71.4)	0.502
Cardiovascular pathology			
Myocardial infarction	4 (14.8)	10 (35.7)	0.075
Cerebrovascular accident	2 (7.4)	4 (14.3)	0.352
Myocarditis	1 (3.7)	1 (3.6)	0.745
Respiratory tract pathology			
Pneumonia	8 (29.6)	5 (17.9)	0.239
Airway obstruction	1 (3.7)	0 (0.0)	0.491
Gastrointestinal tract pathology	1 (3.7%)	0 (0.0)	0.491
Upper gastrointestinal bleeding	1 (3.7)	0 (0.0)	0.491
Sudden cardiac death	10 (37.0)	8 (28.6)	0.502

The issue of mortality in the dementia population exposed to antipsychotics is complex. Meta-analyses of treatment trials of second-generation antipsychotics suggest an increased risk of mortality in the order of 1.5–1.7 times than those not exposed (Schneider et al., 2005; Steinberg and Lyketsos, 2012; Trifiro et al., 2014), while conventional antipsychotics seem to share a risk that is at least as robust (Hales et al., 2007; Trifiro et al., 2007), if not even greater [151, 152]. The complexity of the issue of mortality risk associated with antipsychotic treatment emerges from the observation that the very symptoms that antipsychotic agents are used to control in the dementia population have prognostic significance for the disease course, and have been associated independently with increased mortality. The importance of this observation especially in the context of the current investigation of the association between haloperidol treatment and cause of death is highlighted by the most recent, long-term study of mortality in 957 patients with Alzheimer's dementia [153]. While death was more frequent in those taking first-generation than second-generation antipsychotics, neither class of agents was significantly associated with an increased risk of death when the presence of neurobehavioral symptoms were included in the statistical model. This finding indicates that the neurobehavioral syndromes, as an expression of pathophysiology, may have been a more significant driver of mortality than antipsychotic use. In this first autopsy-based investigation of the cause of unexpected death of psychiatric inpatients hospitalized for dementia with behavioral disturbance, treatment with haloperidol was not associated with an increased risk of sudden cardiac death. Strengths of this study include the consecutive cohort design as well as the unprecedented level of precision of our investigation in ascertaining the compliance with haloperidol treatment and the cause of death. The findings of our study are supported by the fact that the distribution of the causes of death is similar to that recorded after careful clinical investigation in nursing home residents in the USA. The patients who died were on average 81 years old, and the most common final events were sudden cardiac death (25%), myocardial infarction (18%), pneumonia (15%), and thromboembolic or hemorrhagic strokes (7%). The substantial prevalence of sudden cardiac death is expected in the aging heart, as the risk of re-entrant ventricular tachyarrhythmias is increased in areas of myocardial fibrosis [154].

The lack of association between the use of haloperidol and sudden cardiac death in our sample of elderly patients with dementia may be explained by the relatively low dosages of the antipsychotic drug, which was on average 2.2 mg/day, which is equivalent to 110 mg/day of chlorpromazine. In the largest epidemiological study to date, patients receiving prescriptions for haloperidol at the equivalent of <100 mg of chlorpromazine did not show an

excess of sudden cardiac death. In contrast, for those prescribed haloperidol at dosages in the 100–300 mg/day, the incidence risk ratio was 1.92, almost double compared with the control group. The fact that haloperidol was administered only as oral preparation may have also played a role, because a vast majority of cases of haloperidol-related polymorphic ventricular tachycardia torsades de pointes occurred after the intravenous administration of the drug [155].

Although we did not find significant differences in frequency of sudden cardiac death between patients with dementia treated with haloperidol or not receiving antipsychotics, results from our study should be interpreted with caution, given its modest sample size, the absence of data regarding plasma concentrations of psychotropic drugs at the time of death, and lack of data with regard to severity of dementia and functional cardiac reserve. The importance of psychotropic treatment or modifiable cardiovascular disease risk factors as predictors of mortality for progressive, degenerative brain conditions, such as Alzheimer's disease and vascular dementias, has not been conclusively demonstrated. The sample size needs to be put into the context of the meta-analytically derived number-needed-to-harm for an excess mortality due to antipsychotics compared with placebo, which was 100 (95% CI = 50–250) for second-generation antipsychotics. Thus, larger autopsied samples are needed in order to substantiate or refute a possible causal relationship between haloperidol treatment and an increased risk of sudden cardiac death in the elderly with dementia.

3.2 Sudden death in general population

Ifteni P, Barabas B, Gavris C, Moga M, Burtea V, Dracea L. Sudden Cardiac Death: Autopsy Findings in 7200 Cases Between 2001 and 2015. Am J Forensic Med Pathol. 2017 Mar;38(1):49-53

Sudden cardiac death (SCD) is an unexpected event from a cardiac cause [156] affecting million of cases each year with a devastating impact on families and communities. This is a major Public health problem world-wide with a great socio-economic impact [157]. The most used definition stated that SCD is a natural event that occurs within less than one hour from the start of symptoms in individuals without any potentially fatal precondition [158]. The average survival rate is 10.6% and survival with good neurologic function is 8.3%. Nearly one in three victims survives when the arrest is witnessed by a bystander [159] Within the 1- to 40-year age group, the proportion of SCD, noncardiac SD, and sudden unexplained death (SUD) probably differs by age. Because the incidence of premature CAD gradually increases with age, the proportion of other cardiac causes of SD is presumably higher in the lower age groups. Primary arrhythmia syndromes probably dominate in pediatric SD victims, whereas the cardiomyopathies typically manifest during young adulthood.

The incidence of SCD was estimated between 180.00-400.00 cases / year in the United States [160] but in Romania it is still unknown.

In all prior published papers the results showed that men with age between 50 and 69 years are the most affected [6]. The epidemiology of SCD is closely correlated with coronary artery disease (CAD) and up to 80% of the victims have CAD [161]. The most prevalent risk factors which highly increase the risk for SCD are systemic arterial hypertension, diabetes and smoking [162]. In young individuals, the most common diagnoses found in autopsies are hypertrophic cardiomyopathy, coronary artery anomalies, and arrhythmogenic dysplasia of the right ventricle [163]. We have previously conducted studies describing SCD incidence rates and causes of death in persons with schizophrenia [164]. Our autopsy findings indicate that sudden death in schizophrenia is caused by structural cardiovascular, respiratory and neurological abnormalities, with most cases due to acute myocardial infarction. In dementia we conclude that the leading causes of death was myocardial infarction (25.5%) in cases with sudden unexpected death [165] based on autopsy findings. Conduct of an autopsy is essential when trying to identify causes in SCD victims. The recognition of SCD causes is imperative, because previous studies found a hereditary arrhythmogenic syndrome in almost a half of

blood relatives, thereby providing a likely cause of death and identifying surviving relatives at risk from the same fate [167-169].

More information is needed to further improve risk stratification tools and preventive strategies in the future.

Our objective was to describe the characteristics of SCD in Brasov County, Romania over a 15 years period according to the autopsy findings in 6924 cases.

Brasov is on e of the most important city in Romania with a heterogenic population including Romanian, German and Hungarian ethnics. The total population of the area it is around 400,000 inhabitants with an above level of urbanicity compared with the rest of the country.

The local Forensic department is responsible for autopsies of victims of violent and non-violent deaths referred from health service of the city or by the authorities when the autopsy was requested for clarifying the cause of death.

In our study, we assessed the reports of autopsies performed by the local Forensic department between 1 January 2001 and 31 December 2015. For inclusion criteria we defined the sudden unexpected death as the unexpected death within one hour of symptom onset, or in cases of unwitnessed cases as a person last seen alive and functioning well in the 24 hours prior to the event. Data were collected from Brasov County Forensic Department based on registry and death certificates and included cause of death, demographics, comorbidities (medical condition and psychiatric diseases if they are known), time and place of the event, resuscitation maneuvers and blood alcohol concentration. There were excluded all cases with cause of death from another etiology (cerebrovascular accidents, pulmonary embolism, or asthma) as well as homicide, suicide, or incomplete data cases. The study was approved by the Ethic Committee of our institution.

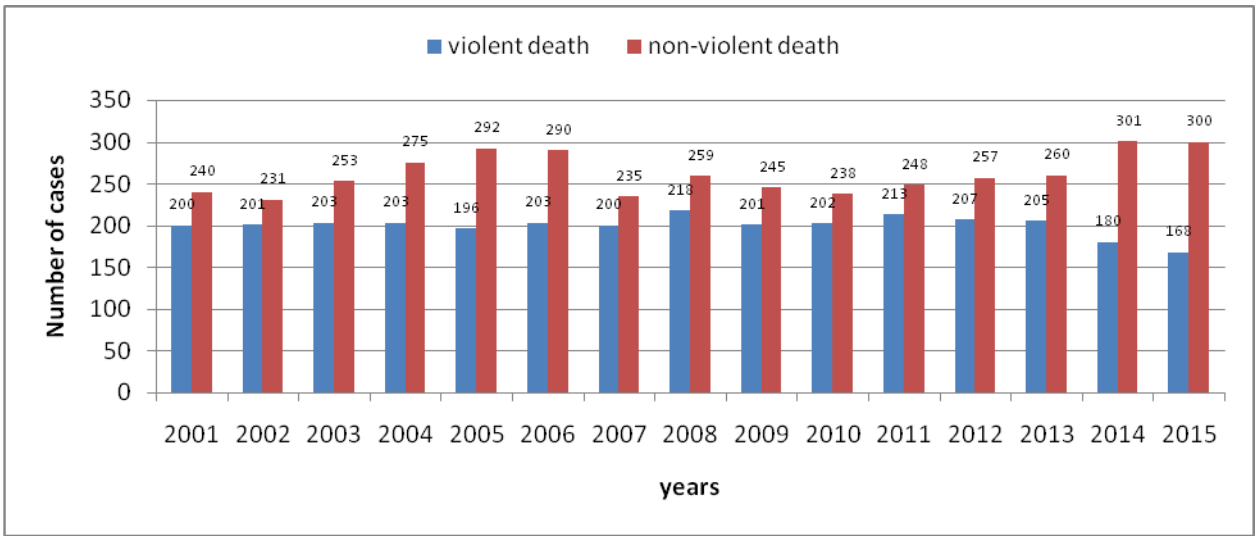
In Brasov County, Romania, all autopsies were performed in Brasov County Forensic Department when examination of the bodies didn't found any conclusive cause or the way of death. During the forensic autopsies all organs are thoroughly examined and toxicology screens are performed in unexplained adolescent and adult cases of sudden unexpected death. Data were written in designated registry and then archived in special places.

Autopsied cases

Between 2001 and 2015, 7200 autopsies were performed in Brasov County Forensic department. For the purpose of the study we excluded 276 cases with incomplete data. Of 6924 autopsies we found 3000 cases with a violent death (68 % accidents, 23% suicides and 9% homicide), 2340 male (78%) with mean age 44.1 ± 13.4 years). The rest of 3924 cases were nonviolent deaths, 2708 male (69%) with mean age 58.7 ± 16.4 years). We noticed that

the number of autopsy performed for violent cases were around 200/year and a tendency of decline starting with 2011 until present (Figure1).

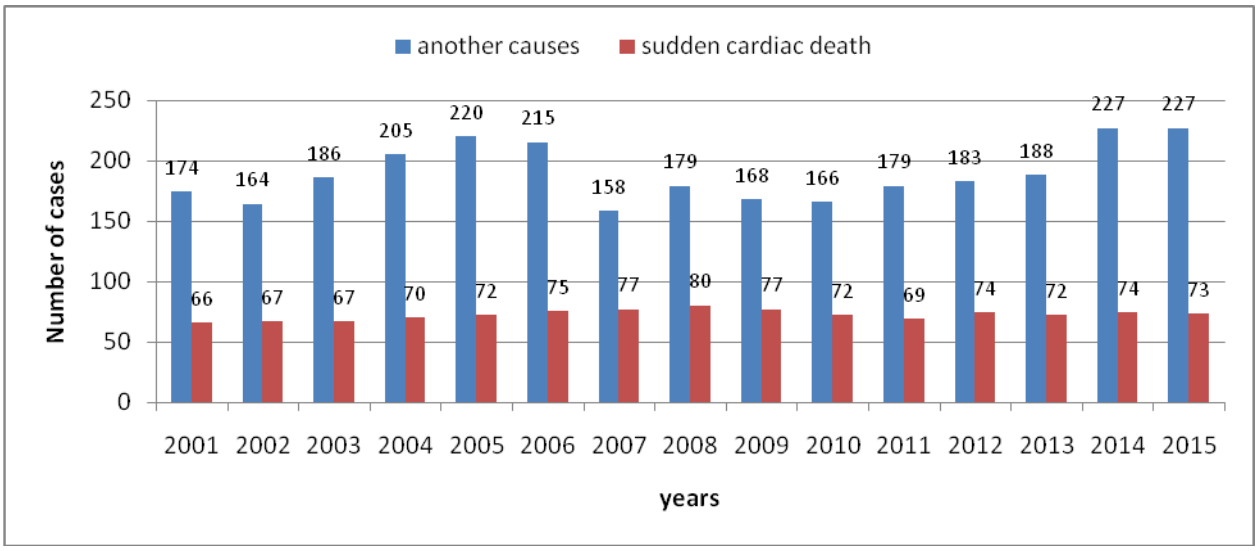
Figure 1. The number of autopsy for violent and nonviolent cases between 2001 and 2015



Sudden cardiac death cases

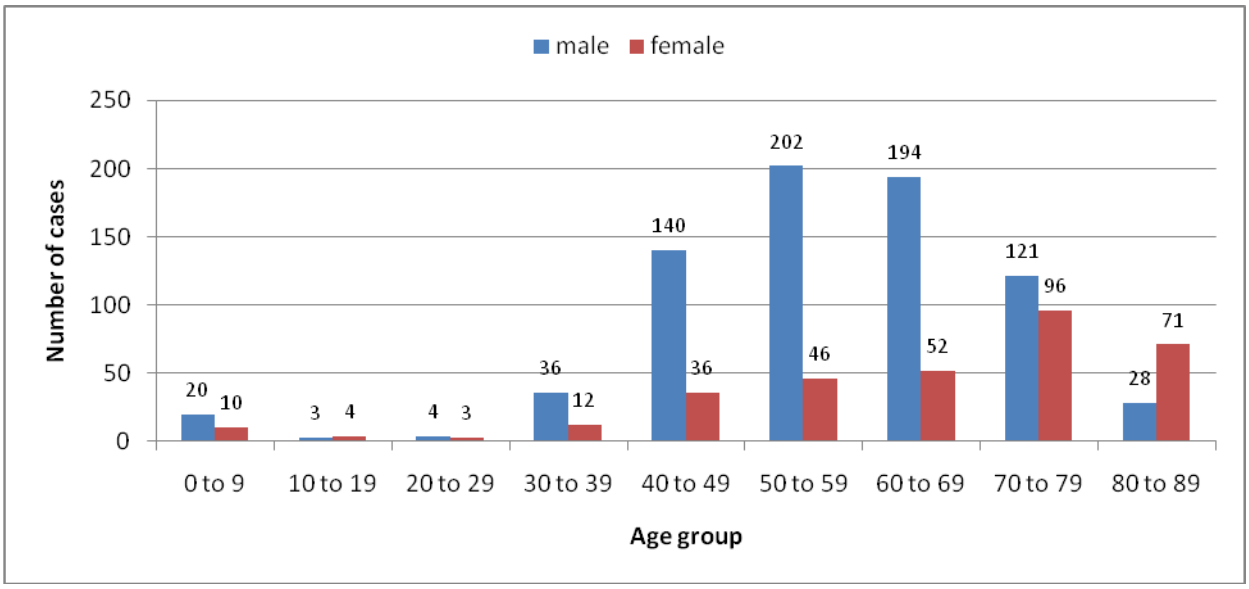
Focusing our research on nonviolent autopsy we found 1085 cases with SCD, 749 male (69%) with the mean age 56 ± 17.4 years and 336 female with mean age 62 ± 13.4 (p<0.01). The average number of SCD was 72.33 cases/year with 66 cases in 2001 (the lowest number) and 80 in 2008 (the highest number). There were two periods with an increased number of autopsies for nonviolent cases: 2002-2005 and 2010-2015 (Figure 2). The incidence of sudden cardiac death was 16/100000 inhabitants.

Figure 2. The number of nonviolent autopsy between 2001 and 2015



Dividing cases in age group we found that 634 autopsy (58.5%) were done for individuals with the age interval between 50 and 69 years old. The vast majority of man with SCD (536 cases) were in the 40-69 years interval (71.5%) in and 219 female were in the 60-89 years interval (65.1%). Age-related distribution of SCD is presented in Figure 3.

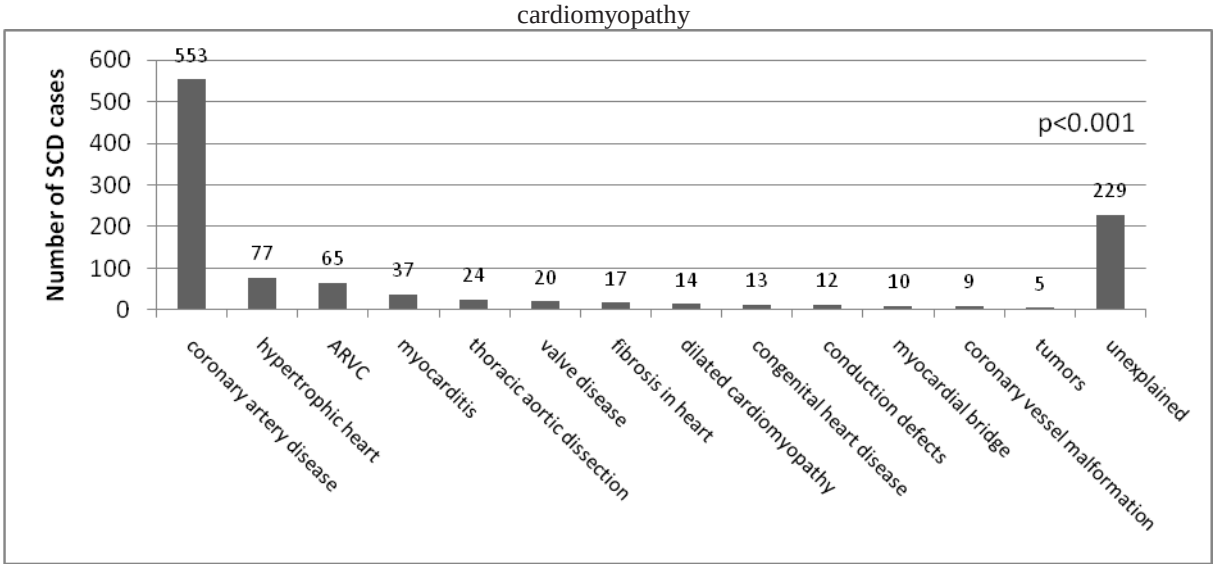
Figure 3. Age-related distribution of SCD



Cause of death

The cause of death was a coronary artery disease in 635 of 1085 (58.5%) autopsied SCD cases followed by hypertrophic cardiomiopathy (77/1085; 7%), arrhythmogenic right ventricular cardiomyopathy (65/1085; 6%), and myocarditis (37/1085; 3%). Another cases included aortic dissection, valve disease, congenital defects and tumors. In 229 of 1085 cases (13.5%), death remained unexplained or not conclusive after autopsy (Figure 4).

Figure 4. Causes of death in the 1085 cases of SCD. ARVC indicates arrhythmogenic right ventricular cardiomyopathy



In 2200 cases of SCD the event occurred at home (56.1%); in 1339 cases, death occurred in emergency rooms (called death on emergency room arrival) in 1339 cases (34.1%). In 237 cases the individuals were found dead (6.0%). In the rest of cases (3.8%) the death occurred during heavy physical activities (lifting or caring weights), and sports (football, climbing, skiing and cycling).

Cardiopulmonary resuscitation

In total, 2145 patients of 3924 received CPR maneuvers (54.6%). In less than 1% cases a specific notification for ''do not resuscitate'' was available. In Brasov County it is mandatory that Public Ambulance Services to send an equipped and trained equipage to every request made trough out 112 call service. Improvement in the health system, with a larger number of ambulances in public service as well as private ambulance company and new emergency rooms in public and private hospitals may be reflected in the increased number of CPR since 2009 reaching the highest percent (59.6%) in 2015. The number of patients survived after a cardiac arrest out-of-hospital remains extremely low (less than 2%).

To our knowledge, this is the first study that characterizes different aspects related to SCD in Romania. The main finding was the high rate of SCD in the group of autopsy for nonviolent death. Regarding the distribution of SCD by gender, the men/woman sex ratio was 69:31. There were no major changes in the pattern over the years. Prior reports showed a men/women ratio of 75:25 [170] with a tendency to equilibrate balance in the recent studies where sex ratio reported was 60:40. The incidence was 16/100000 inhabitants and prior studies reported the SCD incidence between 2/100000 to 40/100000 depending on age,

gender and economic status of the country [171,172]. In the United States the annual incidence of sudden cardiac death during exercise is 1/200000 to 1/250000 in healthy young people [173].

In our study CAD was responsible for most cases of SCD (58.5%), and followed by hypertrophic cardiomyopathy (7%), arrhythmogenic right ventricular cardiomyopathy (6%), and myocarditis (3%). Previous studies have shown that more than 75% of cases of SCD were correlated with preexisting CAD. In 10-15% of cases were identified lesions conclusive for myocardial diseases like hypertrophic cardiomyopathy, idiopathic dilated cardiomyopathy, right ventricular arrhythmogenic dysplasia or infiltrative myocardial diseases [174, 175].

Despite the fact that our results was obtained after a retrospective study we found important risk factors such as diabetes, smoking, obesity and dyslipidemia. One of the most important study showed that age, hypertension, left ventricular hypertrophy, intraventricular conduction block, elevated serum cholesterol, glucose intolerance, decreased vital capacity, smoking, relative weight, and heart rate identify individuals at risk for sudden cardiac death [176]. According to the Framingham study, the annual incidence of sudden cardiac deaths increased from 13/1000 in nonsmokers to almost 2.5 times that for people who smoked more than 20 cigarettes per day [177].

We found an increased number of CPR, year by year, during the study period in Brasov County. In the vast majority of cases the patients with SCD were at home when the event occurred so the critical time for intervention was in many cases exceeded. Despite improving resuscitation practices, in recently published papers on this topic, we found the survival rate for those who suffer an out-of-hospital cardiac arrest (OHCA) between 5 and 10% [178,179]. In many cases, after successful resuscitation, survivors remained with severe neurological impairment [180].

In the Maastricht study, 80% of cardiac arrests occurred at home, and 40% were unwitnessed [181] with low chance of successful CPR.

Our study had some limitation. First, it was a retrospective study and some specific data are lacking regarding events such as complete profile of risk factors for SCD victims, better description of the clinical manifestations presented by victims before death in witnessed cases and CPR procedures performed or autopsy protocols, declaration of relatives, and socio-economic status.

Second limitation is the possibility of absence of entire number of real sudden death cases from autopsy (religion and cultural limitation, extreme ages, misinterpretation of death in hospitals, patients from rural are, etc)

The strength of our study, despite limitations, is the evaluation of a high number of cases during a significant period of time (15 years) in an area with a heterogenic population which made the results generable for an important part of Eastern Europe.

Sudden cardiac death accounted for about more than 25% of all nonviolent deaths in this important urban Romanian community. Based on autopsy reports we found that CAD are the most frequent cause of death, men are more vulnerable in the 6^{th} decade of life. The events occur frequently at home and CPR maneuvers were performed in more than a half of cases. Preventive strategies are needed for lowering this major health problem with huge emotional, social and economical impact.

CHAPTER 2. PROFESSIONAL DEVELOPMENT

2.1. CAREER OVERVIEW

I graduated from the Faculty of Medicine of the University „ Gr. T. Popa'' 'of Iasi in 1999 and I began my specialization in psychiatry in 2002 after residency contest. I worked uninterrupted in Hospital of Psychiatry and Neurology in Brasov initially as a resident from 2002 until 2007, then continuing as a specialist from 2007 to 2012. I became senior psychiatrist in 2012. In recognition of professionalism and organizational capacity I was was named Chief of Clinical 3rd Department in 2015. I am the Chairman of Ethics Committee and Board Member of Hospital Medical Council. In 2016 I was elected as a Director of the Center for fundamental research and preventive strategies in medicine.

I started my research activity clinical trials in 2002, as a member of the clinical trial team coordinated by Mrs. Prof. Univ. Dr. Victoria Burtea. I participated in the most important European study dedicated to the first episode of schizophrenia (EUFEST) led by the European Research Group of schizophrenia. The study primarily aimed to compare the efficacy and safety of treatment with atypical antipsychotics (amisulpride, quetiapine, olanzapine, zyprasidone) compared to haloperidol. The results of this study remain a landmark even after more than 10 years.

I participated as an investigator in more than 20 clinical trials that led to important molecules (SeroquelXR, Zypadhera, Asenapine, etc.) but also to calibrate for Romanian language of valuable assessment scales as PETIT, RDQ, NSI -16, RISA, etc.

I participated as principal investigator in MIN-103 clinical trial to specify efficacy and safety of new molecules for the treatment of schizophrenia.

The clinical activity in a psychiatric emergency department led to the development and publication of two major studies on rapid titration of clozapine in schizophrenia and bipolar disorder. Rapid titration of clozapine has aroused the attention of big names in the world like John M Kane, Christoph U Correll, Peter Manu who agreed to participate as authors in publishing articles in Acta Psychiatrica Scandinavica and Journal of Affective Disorders. Studies showed for the first time worldwide the efficiency and safety of clozapine titration rapid in patients with refractory bipolar I disorder.

Lives of patients with schizophrenia was one of the priorities of my research activity. Starting with the ethical aspects of depot antipsychotic treatment in the first episodes of psychosis and to the treatment of women with schizophrenia who become or want to become pregnant. So we published articles on antipsychotic treatment during pregnancy in patients with

schizophrenia and aspects of involuntary hospitalization of these patients in Therapeutics and Clinical Risk Management and the American Journal of Therapeutics.

Institutionalization of patients with schizophrenia was and still is a theme always present for family and society through the multitude of issues that are involved: ethical, moral, material, human. This traumatic event for the family and patient generate huge cost especially when institutionalized patitents are still young. We performed a study and published results in Revista de Cercetare si Interventie Sociala.

Sudden death of hospitalized patients with schizophrenia, was another concern in research. We wanted to check if antipsychotic treatment may have an impact in these cases. The study we conducted showed that cardiovascular disease is the major cause of sudden death in patients with schizophrenia. The article was published in Schizophrenia Research and is one of the few of its kind presented pathological findings as a source of support.

In collaboration with colleagues from the Faculty of Medicine have managed to publish a comprehensive 15-year study on sudden death in the general population. The study results was published in American Journal of Forensic Medicine and Pathology.

Among future directions for research include efficacy and safety of depot antipsychotics Generation II (second generation long-acting antipsychotics). The first step was taken by highlighting the efficacy of olanzapine long-acting in preventing relapse in schizophrenia with catatonic episodes and publishing the results in the American Journal of Therapeutics.

Another topic for future research is to evaluate the efficacy and safety of clozapine administered to patients with mental retardation for aggressive behaviors.

2.2. PROFESSIONAL DEVELOPMENT AND NATIONAL AND INTERNATIONAL RECOGNITION

A. MEMBERSHIP IN SCIENTIFIC COMMITTEES

I was member in the Scientifiv Committees of two romanian conferences with international participation.

1. A VIII-A CONFERINTA INTERNATIONALA DE PSIHIATRIE ROMANO - MAGHIARA, MIERCUREA CIUC, 22-25 IUNIE 2016.

2.SIMPOZIONUL NATIONAL DE PSIHIATRIE CU PARTICIPARE INTERNATIONALĂ ZILELE DIALOGULUI SOCIAL În cadrul ,,Zilelor Institutului Socola” Iasi, 3-5 NOIEMBRIE 2016

I am also member of the WPA and APPR.

B. BOOKS, MONOGRAPHS

I am the principal author of 3 books and co-author in another one.

1. Burtea V, **Ifteni P.** Psihopatologie - cazuri clinice Editura Universitatii Transilvania Brasov 2014, ISBN:978-606-19-0396-2

2. **Ifteni P**., Taran L. Elemente de diagnostic si tratament in tulburarile depresive. Ed. Univ Transilvania, 2011, ISBN 978-973-598-969-9

3.Taran L., Buicu G., **Ifteni P**., Budan R. Popa C. Actualitati clinico-evolutive ale tulburarilor de spectru bipolar. Ed. University Press Tg. Mures, 2011, ISBN 978-973-169-154-1

4.Szalontay AS, **Ifteni P**. Aspecte practice ale managementului tulburarilor comportamentale in dementa Alzheimer. Editura ,,Gr. T. Popa,, Iasi, 2016

C. CITATIONS

I have 86 citations in Google Scholar.

D. LECTURER AT INTERNATIONAL MEETINGS IN PSYCHIATRY

I was attended at the most important psychiatric congresses in Europe in many cases with posters and oral-presentations.

Rapid Clozapine Titration in Treatment-Refractory Bipolar Disorder, WPA, Madrid, 2014 – oral presentation.

2.3 LEADERSHIP AND MANAGERIAL SKILLS

Since 2015 I am Head of the 3rd Clinical Department, Psychiatry and Neurology Hospital Brasov. I was elected as President of The Ethics Committee of the Hospital and member in the Medical council. Since 2015 I am Vice-Dean at Faculty of Medicne involved in research activities.

CHAPTER 3. ACADEMIC DEVELOPMENT

My academic development combined teaching activities with clinical activities in the Psychiatry and Neurology Hospital Brasov.

My academic career started in 2002 as a Junior Assistant Professor at Transylvania University from Brasov, where I am at present an Associate Professor. Through my academic career I focused on engaging students and residents in psychiatry in the learning process and motivating them to practice higher-level critical thinking skills, while promoting meaningful learning experiences.

2002-2009 Junior Assistant Professor

In 2002 I was admited in Transylvania University from Brasov, Faculty of Medicine, Psychiatry Discipline. As Junior Assistant Professor I delivered practical lessons in the field of clinical psychiatry to the medical students in the 4th year (nurse program) and 6th year (General Medicine). I was involved in more than 10 dissertation thesis and I contributed with one chapter in the ,,*Manual de psihiatrie pentru asistentele medicale*,, by Prof. Dr. Victoria Burtea. I published more than 10 aticles in B and B+ journals.

2009-2012 Assistant Professor

Durring that period I finished my residency in psychiatry, I was employed as specialist in Psychiatry and Neurology Hospital Brasov. I continued the practical lessons in the field of clinical immunology to the medical students and I was involved in theaching process of the new residents in psychiatry.

I continued to supervise more than 10 dissertation thesis while implementing a new approach for creative scientific research to improve students' perception of academic success. The students were stimulated to perform high quality research.

2012-2015 Lecturer

As a lecturer I was involved in more academic activities (nurse program, ERASMUS program). I continued to lecture in clinical psychiatry to the 4th year students in General Nursing and 6th year medical students. In parallel I was involved in the activity of residents in psychiatry.

2015-present Associate Professor

Since 2015 I am Associate Professor at Transylvania University from Brasov, Faculty of Medicine, Fundamental Science Department. I am the coordinator of the ERASMUS program and coordinator of rezidents in psychiatry.

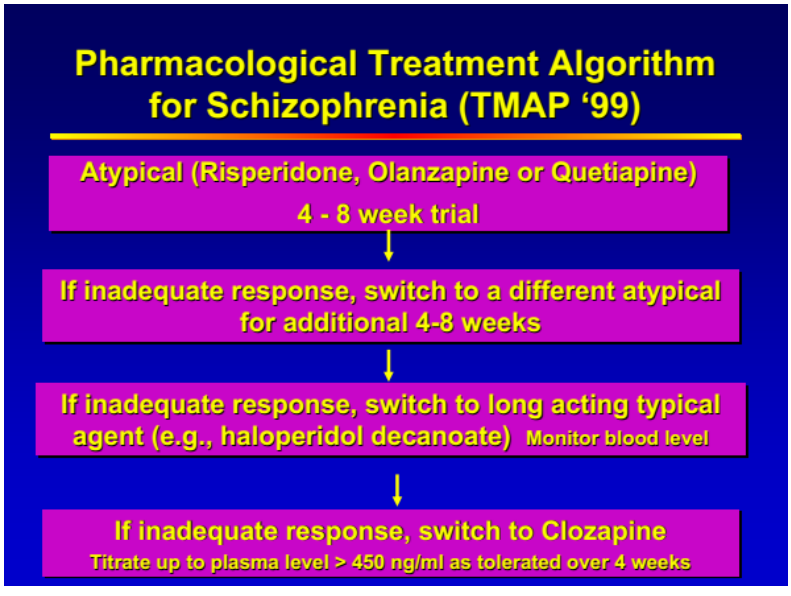
(B-II) THE EVOLUTION AND DEVELOPMENT PLANS FOR CAREER DEVELOPMENT

CHAPTER 1. SCIENTIFIC DEVELOPMENT FUTURE PLANS

LONG-ACTING ANTIPSYCHOTICS IN EARLY STAGE OF SCHIZOPHRENIA

The NICE guidelines (National institute for Health and Care Excellence) recommended the long-acting injectable antipsychotics (LAIs) for people with schizophrenia with poor adherence to treatment, even if they are in the early phases. LAIs are among the most effective treatments in psychiatry, but still remain underutilized in clinical practice. Although LAIs are typically used to maintain treatment adherence in patients with chronic schizophrenia, recent research has suggested that they may also provide an effective treatment strategy for patients with early-phase or first-episode disease.

The evidence review demonstrated that LAIs are superior to placebo for acute and maintenance treatment of schizophrenia and, in general, appear to be similar to one another in terms of schizophrenia relapse prevention. Study design impacts the demonstrated efficacy of LAIs versus oral antipsychotics, but recent database and randomized controlled studies favor the use of LAIs in early-phase schizophrenia patients. LAIs vary considerably in their propensity to cause certain adverse effects, including weight gain, metabolic effects, extrapyramidal symptoms, and prolactin elevation, and these differences can be used to help guide LAI selection. Some studies, but not all, have demonstrated significant reductions in health care utilization or overall costs with LAIs.



The expert panel identified several barriers to LAI use in current practice, including clinician lack of knowledge, negative attitudes about LAIs, and resource and cost issues [182].

Potential advantages and disadvantages of LAIs were presented by the CME Program education of Psychopharmacology Institute [183]

- ✓ Early identification of non-adherence
- ✓ Providing a mechanism for monitoring adherence with injections
- ✓ No need to remember to take medication every day
- ✓ Regular interactions between patient and medical staff
- ✓ Reduced relapse frequency and rehospitalization rates
- ✓ Clear attribution of the cause of relapse or non-response, discriminating between non adherence or lack of response
- ✓ Reduce the risk of accidental or deliberated overdose
- ✓ Treating patients with more stable plasma concentrations than oral medications
- ✓ Avoidance of first-pass metabolism – better relationship between dose and blood level of drug
- ✓ Lower and less frequent peak plasma level – reduced side effects

Potential disadvantages

- ✓ Slow dose titration
- ✓ Longer time to achieve steady state levels
- ✓ Less flexibility of dose adjustment
- ✓ Delayed disappearance of distressing and/or severe side effects
- ✓ Pain at the injection site can occur, and leakage into the subcutaneous tissue and/or the skin may cause irritation and lesions (especially for oily long-acting injectable)
- ✓ Burden of frequent travel to outpatient clinics or home visits by community nurses for their administration
- ✓ Risperidone long-acting injectable needs refrigeration, which may be cumbersome in some latitudes
- ✓ Perception of stigma

Randomized clinical trials evaluating the rate of relapse comparing discontinuation *versus* maintenance

Studies	Sample size	Treatment duration (months)	Discontinuation	Follow up (months)	Rate of relapse placebo *versus* maintenance	LAI (%)
Kane *et al.* [1982]	28	12	–	12	41% *versus* 0%*	Yes
Crow *et al.* [1986]	120	1	Reduce 50% first month Placebo second month	12	46% *versus*62%*	Yes (52.5)
McCreadie *et al.* [1989]	15	24	–	12	57% vs 0%*	Yes
Hogarty and Ulrich, [1977, 1988]	75	–	–	12 24	61% vs 27%* 64% vs 43%*	Yes (30)
Gitlin *et al.* [2001]	53	12	–	6 (3 crossover)	13% vs 1%*	Yes (100)
Gaebel *et al.* [2002]	115	12	50% every 2 weeks	24	42% vs 38%	No
Wunderink *et al.* [2007]	131	6	Step by step (clinical opinion)	18	43% *versus* 21%*	Yes (4)
Chen *et al.* [2010]	178	12	4–6 weeks	12	79% *versus* 41%*	No
Boonstra *et al.* [2011]	20	12	6–12 weeks	6	82% *versus* 12%*	Yes (5)
Gaebel *et al.* [2011]	96	12	3 months	12	19% *versus* 0%*	No

*$p < 0.05$.
FEP, first episode of psychosis; LAI, long-acting injectable.

We will conduct a future project with a mirror image design with 3 major objectives:

1. To evaluate efficacy of LAIs in avoiding the status of treatment resistant schizophrenia;
2. Obtaining remission;
3. Obtaining recovery.

DEVELOPMENT OF PROTOCOLS FOR INTERVENTION IN THE COMMUNITY FOR IDENTIFICATION OF UNTREATED PSYCHOSIS

DUP is generally determined as the time from the onset of psychotic symptoms to the initiation of treatment or first clinical presentation, when a diagnosis of first episode psychosis may be given. The idea that early treatment leads to better outcomes is a standard in medicine. From cancer to coronaries, we find that detection early in the disease course offers better prognosis. The longer a pathological process is left unchecked, the more damage is done; illnesses become more complex, thus they become more difficult to treat. Early intervention in the community with individuals with risk for psychosis may reduce this process.

CLOZAPINE FOR AGITATION IN INTELLECTUAL DISABILITY POPULATION

Antipsychotic medications have been used extensively to treat aggressive behaviours in persons with intellectual disabilities (ID) when the main psychiatric diagnoses given to them in the past were schizophrenia, childhood psychoses and ID with behaviour problems. Today,

antipsychotics are still estimated to comprise 30-50% of all the psychotropics prescribed for persons with ID, although the prevalence of psychotic disorders is only 3% in this population. The overuse of antipsychotics in persons with ID could be justified if their aggressive behaviours were associated with mostly psychotic disorders and not other psychiatric disorders or factors and if the anti-aggressive properties of the antipsychotics have been supported by basic research or reviews of clinical studies.

We intend to develop a program for treatment with small doses of clozapine in ID admitted for of agitation and aggressiveness.

CHAPTER 2.PROFESSIONAL AND ACADEMIC DEVELOPMENT FUTURE PLANS

As a Director of the research affiliated to our department I will support my colleagues in their research projects and in writing papers with results.

As a teacher, I will further try to remain involved as much as I can in active training of the medical students. Our Hospital and University will be the host of examination for specialist and senior psychiatrist qualification.

I will be involved in medical training of foreign students who visited our university through the Erasmus program.

I am the coordinator of the scientific committee for the organization of Scientific Communication Session of The Students of Transilvania University, Faculty of Medicine and I will encourage students to present their works.

Keeping my focus my activity in continue postgraduate training of doctors, both by organizing and participating in continuing medical education courses and by writing books that contribute to raising the level of medical education and thus, the quality of patient care.

PhD coordination and achieving full professorship are envisaged in order to progress with my academic activity in the next years. Through my involvement in coordination of doctoral thesis I will continue to support the young doctors to perform their own researches and to communicate the results of their research in the national and international scientific environment. Early career researches should be strongly supported in preparation of their doctoral thesis through cooperative projects developed with colleagues from related disciplines.

With the help of colleagues from the Faculty of Medicine I will try to resume the tradition of ,,Zilele Medicale ale Brasovului,, and to organize an annual symposium of psychiatry at Brasov.

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