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Review

Pharmacotherapy of Suicidal Behaviour in Major Depression, Schizophrenia and Bipolar Disorder

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A B S T R A C T

The psychopathological dynamics in suicidality overcomes actual diagnostic distribution therefore pharmacotherapy has restricted role in overall prevention of suicidal behaviour among mentally ill and is demanding for clinician. This role is achieved through reduction and alleviation of suicidal risk with rational and individual pharmacotherapeutic approach emphasising effective, safe and tolerable treatment. The genetic and epigenetic factors, dysfunction of neurotransmitter, neuroendocrine system and stress response system has been determining for neurobiology of suicidality. Therefore, pharmacotherapeutic approach should be focused, not only on prevention and reduction of suicidality, but adjusted for general and diagnosis-specific risk factors. Suicidality represents trans-diagnostic issue, however making the correct diagnosis is of great importance. Identical group of psychiatric medications or even the same drug, could be palliating for suicidal behaviour in one diagnostic category and in other aggravating concerning suicidal ideations. Clinician should be reserved towards epidemiological studies about reducing suicidal rate due to increased consumption of antidepressants. Detailed data analysis showed there is no relevancy which antidepressants were given to specific patient, in what age and phase of illness. The FDA has issued warnings about possible increased risk of suicidal behaviour in children and adolescents when given antidepressant therapy. In general, serotoninergic drugs have neutral or mildly protective effect on potential suicidal behaviour while noradrenergic drugs may have activating effect or could even worsen suicidal ideation in certain phase of the illness. When given in appropriate dose and the right time, dual or noradrenergic antidepressants, could also have good protective impact on specific patient. In patients with bipolar disorder, antidepressive drug could be trigger for suicidal behaviour. Greater susceptibility when diagnosing bipolar disorder and broader usage of mood stablizing medications, alone or combined with other psychopharmacotherapy, has the significant role in suppression and elimination of suicidal behaviour. The lithium and sodium valproate are found to be particularly suitable for prevention and elimination of suicidal behaviour along with some other mood stabilizers. Pharmacohterapy of suicidality in patients with schizophrenia represents specific problem. Confirmed drug with anti-suicidal effect, clozapine, is not first choice medication and does not represent general solution for suicidality in schizophrenia. For clinician, the pharmacotherapy of suicidal behaviour consists of skilled individual and rational drug administration accompanied with appropriate psychotherapeutic support.

Key words*: pharmacotherapy, suicidal behaviour, major depression, schizophrenia, bipolar disorder*

Introduction

There is no unique theory or therapeutic method designed for prevention or elimination of suicidal behaviour. The fact how 90% suicide victims have had diagnosed permanent or temporary psychiatric disorder could not be omitted[1]. Suicidal behaviour has been frequently related with these mental disorders: major depression, schizophrenia, bipolar disorder and associated comorbid states. Pharmacotherapeutic measures are being focused on prevention of suicidal ideas, behaviours and elimination of existing suicidality avoiding the act of suicide. Therefore, the pharmacotherapy of suicidal behaviour represents secondary prevention[2]. Psychopathology of suicidality has gone beyond diagnostic classification and has had simultaneously intersected and annihilated dimensions of human existence – spiritual, social and biological. For clinician, pharmacotherapy of suicidal behaviour is being particulary demanding and has limited role in overall suicide prevention for various mental disor-

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ders. With rational and individually adjusted pharmacotherapy focused on efficient, safe and tolerable treatment, the role in alleviating and reducing the suicide risk is being accomplished[3,4]. Also, the genetic and epigenetic factors, dysfunction of neurotransmitter and neuroendrocine system, stress response system have determined the neurobiology of suicidality and should be taken into account. Regardless the psychiatric disorder, the neurobiology differs from one individual to another[5,6]. Pharmacotherapeutic approach focused on prevention and elimination of suicidality should also consider general and diagnosis specific risk factors. The most significant overall risk factors for possible suicidal behaviour among mentally ill are: age under 45 years old, therapeutic resistance, previous hospitalizations, history of suicide among relatives, previous suicide attempts, akathisia, despair, comorbid personality disorder with pronounced features such as impulsivity, aggression and rigidity in thinking. The specific risk factors are being affiliated with diagnosis of mental disorder, specific pharmacotherapy and specific interaction of patient with surroundings[7]. The suicidal behaviour, in this article, has been comprehended according to guidelines of Columbia classification algorithm for suicide assessment (C-CASA) like: suicidal attempts, preparations for suicide as well as active or passive thinking about suicide without immediate preparations for realisation[8,9].

Depression

There is no exclusive connection of suicidal behaviour and suicide with particular diagnostic category, however, the treatment of suicidal behaviour is mostly focused on depressive symptoms. High risk features for suicide are found to be: impulsivity, hostility, anxiety, despair, agitation, anhedony, insomnia, panic attacks, hypersensibility, stress susceptibility, cognitive impairment with certain neurobiological (low serotinine level) and genetic characteristics (gene variations for BDNF and it´s receptor NTRK2)[10–13]. Besides mentioned characteristics, the negative life events and circumstances with depressive potential and other psychosocial environmental risk factors have influenced suicidal on behaviour[14]. Greatest expectations in pharmacologic prevention and treatment of suicidal behaviour are being directed on antidepressants. Clinical and epidemiologic research studies have resulted in multiple controversial reports about anti-suicidal potential of antidepressants in general and drug specific. Some reports confirmed beneficial effect of wide-range antidepressant usage on suicide rate reduction in some developed countires[14]. Based on the contrary reports, the supervisor authority for drug transportation have been alarming for caution when applying antidepressants, especially in younger population. According to Carlsten et all. (2001) report, the suicide rate in Sweden was reduced in time period from 1977 to 1979 and from 1995 to 1997 compared with increased antidepressant consumption[15]. Research in Australia (Hall et al., 2003.) and Hungary (Rihmer et al., 2000.) had given similar results, but still, none direct relation between antidepressant effect on reduced suicide rate in those countries was not determined. For example, in Sweden the usage of antidepressants has grown in elderly and suicide rates reduction has been found in younger population[15]. In Australia, the consumption of antidepressants was increased in all age groups, however, the downfall in suicide rate have been reported only among the elderly[16]. Gibbons et al. (2005) had researched data on completed suicides in USA during years 1996–1998 and there was no relation between antidepressant usage and suicide rate in general and in separate counties[17]. The correlation was found when considering only the SSRI and new generation of antidepressants. Increased consumption of antidepressants resulted in decline of suicide rates in and among counties. Higher suicide rate was recorded with tryciclic antidepressants (TCAs) but not equally in every county. Higher suicide rates and increased usage of tryciclic antidepressants was registered in countries with poorly organized health service and with lower socio-economical status, but this was doubtful due to mentioned various demographic and socio-economical factors[17]. Contrary to these positive reports, there are numerous reports about increased suicidal risk related to antidepressants. Rhimer et al. (2008)[18], have done meta-analysis of controlled clinical studies and found moderately increased risk for suicidal behaviour in patients taking antidepressants compared to those on placebo. This result had probably been marked by limitations of these studies when compared to researched parameters and given research protocols which complicated the flexibile therapeutic approach (early drop-out of patients on placebo, monotherapy, masked bipolar depressions). Certain randomized controlled studies openly doubt the efficacy of antidepressants on suicide risk reduction[19,20]. Increased suicide rate reports of depressive patients taking SSRIs and other antidepressants compared to placebo have motivated the WHO and FDA, to issue a warning for clinicians regarding careful usage of antidepressants during first weeks of therapy due to higher suicide risk. These warnings have reflected on prescribing antidepressants in practice which could have paradoxically increase suicide risk in depressive patients[21]. In addition, recent meta-analysis of 372 double-blind, randomized and placebo controlled studies encompassing 99.231 depressive adults have shown there is undoubtedly lower risk in depressive persons treated with antidepressants in comparison to individuals on placebo. The tendency towards moderate risk increase has been registered among population under 25 years old, and this might be only possible exception[22]. Research results of Danish suicide register and prescribed antidepressants register have contributed to positive impact of antidepressants on suicide risk reduction. According to results of one Danish study, only 10% of depressive persons who had committed suicide were treated with antidepressant one month before suicide[23]. The meta-analysis of 8 large observational studies (Barbui et al., 2009.), encompassing 200.000 patients, have found SSRIs reduce suicide risk and suicidal behaviour in adults, however, the suicide risk has been found to be twice greater

in adolescents[24]. The short term efficacy studies for specific new generation antidepressants (SSRIs) mostly state there is no increased risk of suicidal behaviour,[25,26] moreover the risk is reduced[27,28]. Even when moderaetly increased risk for SNRIs (venlafaxin) exists, this is explained with limitations of the study and the fact that venlafaxine was used to treat patients with refractory depression and comorbidity[29]. In conclusion, the antidepressants in general, especially SSRIs, if being correctly applied, reduce the suicidal risk. Solely, the pharmacotherapy of suicidal behaviour in depressive individuals could not have been adequate if it was not correctly diagnosed and were not considered other factors for suicidal behaviour. The antidepressant treatment could not be successful without proper psychoeducation and psychotherapeutic support along with treatment of comorbid states and full remission maintanace[10]. When all criteria have been satisfied and with carefully selected antidepressant, based on principles of individually adjusted therapy[30], the efficiency of antidepressants in reduction of suicidal behaviour becomes undoubtful. The caution has been recommended during first weeks of treatment because of uneven antidepressant efficiency on particular aspects of depressive disorder or even pharmacologically potentiated effect to specific suicide features. Due to repetitive research results about increased suicidal risk, the special caution has been suggested while treating children and adolescents in the first months of therapy. For this reason, in year 2004, the manufacturers of antidepressants have been given order from FDA to excerpt a drug declaration warning for professionals on increased suicidal risk for children and adolescents. The American Psychiatric Association (APA) has responded that antidepressants save human lives and is recommended to treat children and adolescents with antidepressants due their favourable effect than deprive them for such treatment. The Texas algorithm for child treatment has (supplemented in year 2006) recommended the SSRIs as a first choice during first and second treatment attempt[31]. In case the child has not shown adequate improvement on second SSRI, then could be considered other categories of antidepressants could be considered. It is also mentioned how combination of two antidepressants, antidepressant and anxiolytics (especially at the beginning of treatment) or some other supportive strategies could enhance the therapeutic response[32,33].

Schizophrenia

Patients with schizophrenia often share many risk factors with general population and persons with other mental disorders. They often commit suicide under influence of symptoms of primary disease and comorbid states and because of that pharmacotherapy represents significant support in prevention and elimination of suicidal behaviour[34,35]. Neurobiological predictors of suicidality, common to other psychiatric disorders, have been basis for pharmacotherapy of suicidal behaviour in schizophrenia and could be amended with such therapy. These predictors are: low serotonin level in central nervous system and low level of serotonin metabolites in cerebrospinal fluid, decreased binding of radioactive marked ligands on pre-synaptic serotonine receptors in frontal cortex and increased density of post-synaptic 5-HT2 receptors in the same brain areas. This serotonin disbalance in central nervous system predisposes primarily impulsive and aggressive behaviour than suicide itself[36]. Recently, the role of gene polymorphism is being researched, particularly genes regulating dopamine transport in patients with schizophrenia and suicidal behaviour[37]. Still, there are many steps to be made in order to complete the neurobiology circle of suicidality in schizophrenia. For this reason, the pharmacologic prevention and therapy has been relying mostly on principles of good clinical practice while treating this disorder and comorbid states. These principles have been appreciative towards early diagnosing and treating schizophrenia, appliance of effective and tolerable antipsychotics, patient education about the illness and pharmacotherapeutic agents, the assurance of compliance and patient supervision during acute phase treatment and after hospital discharge with psychotherapeutic and psychosocial support in order to protect the patient from further stress[34,38,39]. Implementation of these general measures could significantly reduce suicidal risk and create supportive envirnoment for additional efficacy of medications. The discrepancies in appliance of these measures are being preclusive for statisti- cally obvious advantage of certain psychopharmacs on suicidal behaviour reduction in schizophrenia. Some research shows there is no certain evidence about efficacy of second generation antipsychotics in preventing suicidal behaviour in schizophrenia when compared to first generation antipsychotics[40]. The pharmacodynamic characteristics of second generation antipsychotics have ensured: good efficiency, the dopamine-serotonin concept of action with less akathisia and iatrogenically induced depression, better affective stability and cognitive functioning accompanied by better tolerability and compliance. This, with all the other measures for prevention and therapy of suicidal behaviour in schizophrenia, has represented additional significant contribution for suicidal risk reduction[41]. However, the clozapine has been recognized as exception regarding anti-suicidal potential. The study of Meltzer and Okayli (1995) first has shown clozapine reduced suicidal risk in patients with schizophrenia[42]. Aim of the research was to identify whether clozapine therapy reduces suicidality in treatment resistant patients with schizophrenia and schizoaffective disorder. The clozapine had been administred during hospitalisation with average dose of 500 miligrams. When the 2 years period before treatment with clozapine has been compared to period of 2 year treatment with this drug, the reduction of suicidal attempts for 86% during treatment was found. Large two-year multricentric, randomized, prospective, single-blind InterSePT study (The International Suicide Prevention Trial) in which have been compared anti-suicidal effect of clozapine (300–900 mg/ daily) and olanzapine (10–20 mg/daily) confirmed clozapine efficiency in reduction of suicidal risk[34,43]. Meltzer presumed, the fa-

vourable anti-suicidal effect of clozapine could be explained with stabilization of biogenic amines transport in prefrontal cortex because the imbalance of these amines represented the biological basis of suicidality. Clinically, the clozapine has anti-agressive and antidepressive effect, it rarely causes akathisia and is well tolerated therefore has been recommended as first choice medication for prevention of suicide in schizophrenia. Based on Inter SePT research results, the FDA has approved new indication for clozapine – recurrent suicidal behaviour for patients with schizophrenia and schizoaffective disorder. This was the first time FDA approved medication with indication for suicidality. Previously regulated commitment of periodic white blood cells monitoring has remained. Reduction of suicidal risk requires particular skill in treating other comorbid disorders in schizophrenia, most often affective, due caution needed when applying anxiolitycs, antidepressants and mood stabilizing medications. Finally, the most important aspect of suicide risk reduction in schizophrenia lies in well chosen and individually adjusted therapy although pharmacotherapy alone should not be the only support during treatment. It is necessary to become acquainted with patient´s surroundings, medical history, his expectations and expectations of his enviroment in order to ensure the life worth living aided by psychotherapy, psychosocial support and other interventions[34].

Bipolar Disorder

The bipolar disorder is diagnostic category with the greatest suicidal risk. The estimations have shown that 25–30% of individuals with bipolar disorder would have suicide attempt and every fifth individual would commit suicide during lifetime[44]. Suicide risk is over 20 time greater than in general population[45]. Acceptance of distended diagnostic criteria in diagnosing specific subtypes of bipolar disorder (Bipolar disorder I = manic-depressive disorder, Bipolar disorder II = depression with spontaneous hypomania and Bipolar disorder spectrum = depression + bipolar predictors)[46], has revealed the life burdened with severe suicidal risk in this disorder and explications of some authors on increased suicidal risk during antidepressant therapy have been recognized. Usage of antidepressants in bipolar disorder could be a trigger for unwanted and uncontrolled affective changes which might even result in agitation and suicide realization. The distended diagnosing of bipolar disorder (bipolar I and bipolar II) and especially bipolar spectrum subtype has burdened this disorder with increased suicidal risk. This diagnostic category now comprehends significant number of depressive episodes + diagnosis of bipolar depression in first relatives, antidepressant induced mania or hypomania, hyperthymic or cyclothymic temperament, recurrent severe depression episodes (>3), brief severe depressive episodes (on average, <3 monthly), atypical symptoms of depression and severe psychotic depressive episodes, early onset of severe depressive episode (<25 year old), postpartum depression, seasonal depression, rapid cycling behaviour pattern, unstable mood, inefficiency of antidepressants (only acute response, instead prophylactic one), absence of therapeutic response on three or more antidepressants, mixed depression (psychomotor agitation, irritability, verbiage), drug abuse[46,47]. In these mentioned states, antidepressants should be given in combination with mood stabilizing drugs. The selective serotonin reuptake inhibitors have been considered as particularly safe[48]. During acute phase of illness the suicidal risk is especially high and some predictive factors are: stressful life events, hazardous behaviour in bipolar I (often car accidents etc.), the inclination towards hypomanic or psychotic state as well as impulsivity and aggression[49,50]. As significant suicide risk factors and being particularly inherent in bipolar disorder the affective instability, impulsivity and aggressiveness have given the mood stabilizing medications special role in treatment of bipolar disorder and elimination of suicidal risk. Lithium, the medication used in psychiatry since year 1949 as mood stabilizer, had been firstly recognized for anti-suicidal potential. Therapeutic effectiveness in bipolar disorder does not necessary imply drug efficiency in reducing suicidal risk. The lithium has been proven in reducing suicidal risk in bipolar disorder[51,52]. Ten years ago there has been growing evidence, based on parallel studies, on how other mood stabilizing drugs particularly anticonvulsants (divalporex, carbamazepin) show almost equal potential in reducing suicidal risk. The suicidal behaviour, after therapy withdrawal, had increased 16 times equally in patients trea- ted with lithium and in patients taking anticonvulsants[53,54]. Bipolar patient´s who are being, for whatever reason, treated only with antidepressants have particularly high suicide risk and should be monitored during treatment. Yerevanian et al., in year 2007, have been comparing patient groups on mood stabilizing drugs (lithium, divalporex, carbamazepin) with the groups taking mood stabilizing drug + antidepressants and just antidepressants[54]. Key findings of this study were, the suicidal behavior in patients on combined therapy of mood stabilizers and antidepressants was 2–3 times more often than in those who received only mood stabilizer, and as much as 6–10 times more frequent in the group who had received only antidepressants[55]. Likewise, often necessary appliance of antipsychotics in bipolar disorder requires careful selection and monitoring of these patients. The suicide risk in patients who have been receiving combination of antipsychotics and mood stabilizers becomes 5 times higher and in those receiving only antipsychotics as much as 10 times higher than in bipolar patients soley on mood stabilizers[56]. In this case, the most suitable drug combination has expected to be mood stabilizers and second generation antipsychotics, particularly ones with low potential of inducing akathisia and pharmacologic depression. In refractory cases with obvious suicidal risk are best combined clozapine and mood stabilizer. It must not be forgotten, the possibility of pharmacotherapy in reducing and eliminating suicide risk has been limited with the fact suicidality being complex cross-category biopsychosocial phenomenon. The bipolar patients should also be

given, besides pharmacotherapy, structured psychosocial treatment or broader psychotherapeutic support with psychosocial intervention especially during period of prolonged treatment[57].

Conclusion

There is no unique theoretic explanation or therapeutic method for prevention of suicidal behaviour. The pharmacotherapy of suicidal behavior has limited role for mentally ill patients. This role has been primarily achieved by reducing and mitigating the suicide risk through rational and individually adjusted pharmacotherapy focused on effective, safe and tolerable treatment. During treatment of depressive disorder, the antidepressants in general and especially SSRI-s, if properly implemented reduce risk of suicide. Caution is usually advised in the first few weeks, and in children and adolescents in the first months of therapy, because of initial uneven antidepressant effect on specific aspects of depressive disorder with possible transient pharmacogenic potentiation of suicidal risk. The pharmacodynamic features of second generation antipsychotics have ensured treatment of schizophrenia with: good efficiency, dopamine-serotonin concept of action with less akathisia and pharmacogenic depression, better affective stability and cognitive functioning followed by enhanced tolerability and compliance. The clozapine stands as an exception for it´s anti-suicidal potential. It has good anti-aggression and antidepressive action, rarely causes akathisia and is well tolerated therefore it has been recommended as the drug of choice for alleviation of suicidal risk in schizophrenia. The lithium has been proven for reduction of suicidal risk in patients with bipolar disorder. Ten years ago, based on comparative studies, growing evidence highlighted how some mood stabilizers from the group of anticonvulsants (eg. divalporex and carbamazepine) were equally powerful in reducing suicidal risk. If antidepressants or antipsychotics had been prescribed for the bipolar disorder, then it was recommended to prescribe mood stabilizer with them. In addition to pharmacotherapy, in all three diagnostic groups was recommended, to provide a structured psychosocial treatment or psychotherapeutic support with psychosocial interventions, particulary during phase of prolonged treatment.

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FARMAKOTERAPIJA SUICIDALOG PONAŠANJA OBOLJELIH OD DEPRESIJE, SHIZOFRENIJE I BIPOLARNOG POREMEĆAJA

S A Ž E T A K

Farmakoterapija suicidalnog ponašanja je za kliničara vrlo zahtjevna i ima ograničenu ulogu u sveukupnoj prevenciji suicida oboljelih od mentalnih poremećaja, jer suicidalnost nadilazi dijagnostičku podjelu i slijedi vlastitu psihopatološku dinamiku. Ta se uloga najvećim dijelom ostvaruje ublažavanjem i uklanjanjem rizika suicidalnosti putem racionalne i individualno prilagođene farmakoterapije usmjerene na učinkovito, sigurno i podnošljivo liječenje. Treba ipak voditi računa o neurobiologiji suicidalnosti koja je određena genetskim i epigentskim faktorima, disfunkcijom neurotransmitorskog i neuroendokrinog sustava i sustava odgovora na stres. Zato farmakoterapijski pristup usmjeren na prevenciju i uklanjanje suicidalnosti treba prilagoditi kako o općim tako i za dijagnozu specifičnim faktorima rizika. Premda je suicidalnost transkategorijski fenomen, od izuzetne je važnosti postavljanje pravilne dijagnoze, jer ista skupina psihofarmaka ili čak isti psihofarmak, kod jedne dijagnostičke kategorije može ublažiti suicidalnost, a kod druge je potencirati. Zato rezultate nekih epidemioloških studija o smanjenju stope suicida nakon porasta potrošnje antidepresiva, kliničar treba uzeti s rezervom. Detaljnijom analizom dobivenih podataka, može se primijetiti kako ipak nije svejedno koje antidepresive dajemo kojim bolesnicima, u kojoj dobi i u kojoj fazi bolesti. FDA posebno upozorava na mogućnost porasta rizika od suicidalnog ponašanja pri primjeni antidepresiva kod djece i adolescenata. Općenito uzevši, serotoninergička sredstva imaju neutralni ili blago protektivni učinak na pojavu suicidalnog ponašanja dok noradrenergička sredstva mogu imati i aktivacijski učinak, odnosno čak pogoršati suicidalnost u određenoj fazi poremećaja. To ne znači da kod konkretnog bolesnika, noradrenergički ili dualni antidepresiv, ordiniran u pravo vrijeme i u pravoj dozi, neće imati dobar antisuicidalni učinak. Nadalje, primjena antidepresiva kod osoba s bipolarnim poremećajem, može također imati aktivacijski učinak na suicidalno ponašanje. Zato inzistiranje na većoj osjetljivosti za dijagnostiku bipolarnog poremećaja i na široj primjeni stabilizatora raspoloženja, samih ili u kombinaciji s drugim psihofarmacima, ima značajnu ulogu u sprečavanju i uklanjanju suicidalnog ponašanja u toj dijagnostičkoj kategoriji. Pritom se kao posebno pogodni za prevenciju i uklanjanje suicidalnog ponašanja navode litij i natrijev valproat, ali i neki drugi stabilizatori raspoloženja. Poseban problem predstavlja farmakoterapija suicidalnosti u oboljelih od shizofrenije. Premda je klozapin potvrđen kao sredstvo s antisuicidalnim učinkom, taj lijek ne spada u prvu terapijsku liniju i ne može biti opće rješenje za problem suicidalnosti u shizofrenih. Farmakoterapija suicidalnog ponašanja ostaje za kliničara i dalje usko vezana uz umijeće racionalne i individualno prilagođene primjene psihofarmaka, popraćene odgovarajućom psihoterapijskom podrškom.