

## PSYCHOPHARMACOTHERAPY PRESCRIPTION AND SUICIDAL BEHAVIOUR

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### SUMMARY

Suicidal behaviour has multiple causes. Psychiatric disorder is a major contributing factor. Consecutively, diagnosis and treatment of mental disorders has an impact on suicide rate. The studies that investigated the possible impact of psychopharmacotherapy prescription practise on suicide rate have been gathered in the present article. Ongoing discussion of potential benefits and risks of antidepressant treatment with respect to suicidal behaviours includes many ecological, or population- based, correlational studies of temporal or regional trends in suicide rates and rates of usage of modern antidepressants including SSRIs. A number of studies have found a relationship between increase in national antidepressant prescribing and declining suicide rates, with general agreement but some exceptions. In general, studies showed that increased prescribing of antidepressants may indicate improved diagnosis and treatment of depression. On the other hand, studies that investigated the impact of prescription of anxiolytics on suicide rate were scarce, although the ratio of anxiolytics to antidepressants has been described as a quality indicator regarding treatment of depression, which is in most cases combined with anxiety and increased suicide risk. Importantly, sedatives and hypnotics are widely prescribed to elderly persons with symptoms of depression, anxiety, and sleep disturbance, but studies demonstrated that sedatives and hypnotics were both associated with increased risk for suicide in the elderly. Finally, studies on antipsychotic prescription demonstrated that particularly treatment with clozapine decreased suicide mortality among individuals with schizophrenia and schizoaffective disorders and on the other hand lithium reduced suicide rate among individuals with mood disorders.

**Key words:** suicide rate – antidepressants – anxiolytics – antipsychotics - depression

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### INTRODUCTION

Suicide is a significant public health problem (Levi et al. 2003). Approximately 1 million people are estimated to die because of suicide each year in the world (Yoshimasu et al. 2008). Suicidal behaviour has multiple causes. Psychiatric disorder is a major contributing factor. Consecutively, diagnosis and treatment of mental disorders has an impact on suicide rate (Mann 2002, Kapusta et al. 2010). Nevertheless, psychopharmacotherapy play rather a minor role in most suicide prevention strategies (van der Feltz-Cornelis et al. 2011).

The studies that investigated the possible impact of psychopharmacotherapy prescription practise on suicide rate have been gathered in the present article.

### ANTIDEPRESSANTS

Depression is one of the most common psychiatric disorders in society and one of the most important risk factors for suicide (Arsenault-Lapierre et al. 2004, Nock et al. 2010, Bernal et al. 2007). Treatment of depression might prevent suicide. A number of studies have found a relationship between increase in national antidepressant prescribing and declining suicide rates (Gibbons et

al. 2005, Barak & Aizenberg 2006, Henriksson et al. 2006, Bramness et al. 2007, Korkeila et al. 2007, Nakagawa et al. 2007, Kalmar et al. 2008, Guaiana 2011, Guaiana et al. 2011, Gusmao et al. 2013), with general agreement but some exceptions (Baldessarini et al. 2007). Antidepressant use has continually increased in most European countries since the advent of SSRIs (Svab et al. 2011, Isacson & Rich 2011, Organisation for Economic Cooperation and Development 2012). From 1995 to 2010 decrease in suicide rate was observed across the EU-27 countries, with only the exceptions of Malta, Poland and Portugal where increasing trends were present (Organisation for Economic Cooperation and Development 2012). A recent study by Gusmao and co-workers researched the association between the use of antidepressants and incidence of suicide in European, largely EU, Member States between 1980 and 2009. They observed an inverse correlation between recorded standardised death rate (SDR) for suicide and antidepressant defined daily dosage (DDD) in 28 European countries (Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxemburg, Netherlands, Norway, Poland, Portugal, Romania, Slo-

vakia, Slovenia, Spain, Sweden, Switzerland and United Kingdom), with the exception of Portugal. Variability was marked in the association between suicide and alcohol, unemployment and divorce. Every unit increase in DDD of antidepressant per 1000 people per day, adjusted for these confounding factors, reduced the SDR by 0.088 (Gusmao et al. 2013). Many individual studies also showed a positive impact of antidepressants prescription on suicide rate in different European countries. Kalmar has shown that in Hungary the suicide rate correlated negatively with an increased use of antidepressants in both genders and the strongest association was found in the oldest age groups, where the increase in antidepressant use was highest. Antidepressant rate predicted suicide rate after controlling for some relevant socio-economic factors such as divorce rate and unemployment rate (Kalmar et al. 2008). Furthermore, Sebestyen analysed the relationship between increasing antidepressant utilization and national suicide rate of Hungary between 1998 and 2006, with particular regard to seasonal patterns and gender differences. He found that increasing antidepressant utilization was associated with decreased seasonality of suicides among males and the results suggested that decreasing seasonality of suicides could be a good marker of lowering rate of depression-related suicides in the population particularly among males (Sebestyen et al. 2010). Korkeila analysed the associations between use of antidepressants and suicide rates in Finland and concluded that an increase in the use of antidepressants may decrease the suicide rate in Finland (Korkeila et al. 2007). Furthermore, Salokangas reported that, at the national population level in Finland, increased use of antidepressants in women was associated with a decreased suicide rate in men. He hypothesised that increased use of antidepressive medication in women led to a decrease in stress and depressiveness in their microsocieties, thereby also reducing the risk of suicides in men belonging to their close social network (Salokangas et al. 2012). Bramness has shown that the fall in suicide rate in Norway and its counties was related to the increased sales of non-tricyclic antidepressants (Bramness et al. 2007). Henriksson also reported a trend linking a greater prescription of antidepressants with fewer suicides in Sweden (Henriksson et al. 2006). Guaiana investigated the trend in antidepressant prescribing and deaths by suicide in Emilia Romagna, a large Italian region and reported that overall suicide rates decreased during the period under examination which was characterised by an exponential increase in the use of antidepressants (Guaiana 2011). Then, in United States, Gibbons examined the association between antidepressant medication prescription and suicide rate by analysing associations at the county level across United States. A positive association between tricyclic antidepressant prescription and suicide rate was observed. By contrast, increases in prescriptions for selective serotonin reuptake inhibitors (SSRIs) and other new-generation non-SSRIs were associated with lower

suicide rates both between and within counties over time and might reflect antidepressant efficacy, compliance, a better quality of mental health care, and low toxicity in the event of a suicide attempt by overdose (Gibbons et al. 2005). In Japan, Nakagawa reported that annual increases in prescribing of newer antidepressant medications, (mainly SSRIs) were associated with annual decreases in suicide rates, particularly among males (Nakagawa et al. 2007). On the other hand, in Israel, an overall reduction in suicides, which was significant only in elderly men, was noted in association with increased rates of antidepressant prescription (Barak & Aizenberg 2006). Whereas epidemiological studies have tended to show an association of lower rates of suicide with higher rates of antidepressant use (Gibbons et al. 2005, Barak & Aizenberg 2006, Henriksson et al. 2006, Bramness et al. 2007, Korkeila et al. 2007, Nakagawa et al. 2007, Kalmar et al. 2008, Guaiana 2011, Guaiana et al. 2011, Gusmao et al. 2013), clinical trials of antidepressants in children and adolescents have shown an increased risk of suicidal thoughts or behaviour relative to those who received placebo (Hammad et al. 2006, Hassanin et al. 2010).

The concern above led to US and European Regulators issuing warnings regarding the prescription of SSRI Antidepressants to children and adolescents and the risk of increased suicidal ideation and behaviour [ as opposed to completed suicides]. Controversially, it was shown that whereas as a consequence of this warning in both US and Netherlands the rate of antidepressant prescribing in this young age group reduced, the number of completed suicides in both countries for this age group actually increased (Gibbons 2007). Though there was some controversy about these findings (Jureidini 2007, Olfson 2007), it seems important to note that there is a difference between increased suicidal ideation and behaviour and completed suicide and that there must be concern if a measure aimed at reducing suicide, such as the regulators's warning actually appears to be associated with the opposite effect. Olfson has pointed out some other factors which may have come into play as a result of the warning, such as 'an increase in prescriptions of non-SSRI antidepressants to youth as physicians searched for alternative treatments' (Nemeroff 2007).

Interestingly, a British studies have not found an increased rate of suicide in young persons related to the reduction in SSRI prescribing consequent on the regulatory warnings. (Wheeler 2008) Indeed, there has been a reduction in the suicide rate of young men in the UK in recent times (Biddle 2008) It has been pointed out (Simon 2008) that the intention of the regulators was not to stop the prescription of SSRIs where indicated, but that SSRIs should be prescribed when indicated and that psychiatrists should regularly follow up patients to whom SSRIs have been prescribed. Simon has also commented that 'the most recent US

data suggest that youth suicide rates have begun to decline again, so the earlier finding of an increase may just be coincidence.' (Simon 2008).

There is a longstanding belief that antidepressants might have an early "activating effect" that gives depressed patient the energy to follow through on suicidal impulses before the mood improvement also provided by antidepressant treatment takes effect. Then the meta-analysis of 372 double blind randomised placebo controlled trials of 12 marketed antidepressant product (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, and venlafaxine) demonstrated that risk of suicidality associated is strongly age dependent. Compared with placebo, the increased risk for suicidality and suicidal behaviour among adults under 25 approaches that seen in children and adolescents. The net effect seems to be neutral on suicidal behaviour but possibly protective for suicidal ideation in adults aged 25-64 and to reduce the risk of both suicidality and suicidal behaviour in those aged >65 (Stone et al. 2009).

## ANXIOLYTICS

Studies that investigated the impact of prescription of anxiolytics on suicide rate are scarce (Melander et al. 1991, Ekedahl et al. 1993, Carlsten et al. 2009), although the ratio of anxiolytics to antidepressants has been described as a quality indicator regarding treatment of depression, which is in most cases combined with anxiety and increased suicide risk (Ciuna et al. 2004). Carlsten examined whether specific types of psychoactive drugs were associated with suicide risk in late life, after controlling for appropriate indications. The study demonstrated that after adjustment for affective and anxiety disorders neither antidepressants in general nor SSRIs showed an association with suicide. Antipsychotics had no association with suicide after adjustment for psychotic disorders. On the other hand, sedatives and hypnotics were both associated with increased risk for suicide after adjustment for appropriate indications. Given the extremely high prescription rates, a careful evaluation of the suicide risk should always precede prescribing a sedative or hypnotic to an elderly individual (Carlsten et al. 2009).

An interesting study on suicide among US physicians revealed mental illness as an important comorbidity for physicians who completed suicide but post-mortem toxicology data showed low rates of medication treatment. Physicians who had completed suicide compared to non-physicians who had completed suicide were more likely to have antipsychotics, benzodiazepines and barbiturates present on toxicology testing but not antidepressants (Gold et al. 2013).

## ANTIPSYCHOTICS AND LITHIUM

Studies demonstrated a close relationship between schizophrenia and suicide and particularly the presence of depression and depressive features was associated with an increased risk of suicidality in patients with schizophrenia (Balhara 2012). On the other hand, the literature concerning the net effect of antipsychotic medication on suicidality in patients with schizophrenia is not consistent (Aguilar & Siris 2007). A good profile to treat hostility, impulsivity, and depression while not provoking extrapyramidal side effects is crucial when choosing antipsychotics in the presence of suicide risk (Aguilar & Siris 2007). The studies demonstrated that the strongest and perhaps unique evidence has been shown for clozapine, which seems to have a clinically relevant advantage over both first- and second-generation antipsychotics for reducing suicidality (Meltzer et al. 2003, Alphas et al. 2004, Aguilar & Siris 2007). The International Suicide Prevention Trial was a multi-centre, randomised, 2-year study conducted to investigate the effectiveness of clozapine for reducing suicidal behaviour, among individuals with schizophrenia and schizoaffective disorders who were preselected to be a high risk for suicide but were not otherwise treatment-resistant demonstrated that clozapine reduced suicide risk in patients with schizophrenia or schizoaffective disorder (Alphas et al. 2004). In a recent updated systematic review and meta-analysis 48 randomised controlled trials comparing lithium with placebo or active drugs in long term treatment for mood disorders regarding prevention of suicidal behaviour were included (Cipriani et al. 2013). It was found that lithium was more effective than placebo in reducing the number of suicides and deaths from any cause (Cipriani et al. 2013). However no clear benefits were observed for lithium compared with placebo in preventing deliberate self-harm. It was also observed that in unipolar depression, lithium was associated with a reduced risk of suicide and also the number of total deaths compared with placebo (Cipriani et al. 2013).

## CONCLUSIONS

We reviewed the studies that investigated the possible impact of psychopharmacotherapy prescription practice on suicide rate in different countries in the world. First of all, a number of studies have found a relationship between increase in national antidepressant prescribing and declining suicide rates as increased prescribing of antidepressants may indicate improved diagnosis and treatment of depression. This effect of increased antidepressant prescribing reducing suicide rate became visible once the availability of safe antidepressants such as SSRIs was established, as opposed to the cardiotoxic tricyclics. Nevertheless,

particularly in young persons, Patients prescribed SSRIs should have an appropriate indication for the prescription and should receive appropriate follow up. Secondly, studies that investigated the impact of prescription of anxiolytics on suicide rate were scarce, but the studies demonstrated that sedatives and hypnotics were both associated with increased risk for suicide, particularly in the elderly. Finally, studies on antipsychotic prescription demonstrated that particularly treatment with clozapine decreased suicide mortality among individuals with schizophrenia and schizoaffective disorders.

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