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Treatment of suicidal behaviours by pharmacotherapeutic means

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Background

Suicidal behaviors are not diseases[1], but we can attempt to reduce the occurrence of these behaviours through treating underlying psychiatric and circumstantial problems with medications and other interventions, and monitor changes and developments in suicidality closely during the course of treatment. The key goal in any intervention or study is to prevent or minimize suicide attempts or deaths[2]. However there are few randomized clinical trials that have systematically investigated suicide as an end point or outcome measure, and therefore formal evidence of efficacy of pharmaceuticals in reducing suicidal behaviours is limited[3]. The purpose of this review is to investigate the current evidence-base of pharmaceuticals used for treatment of suicidal behaviours.

Methodology

A systematic literature search was performed in the Pubmed/MEDLINE and Scopus databases. Three keyword searches were performed in both databases: suicid* AND pharmacotherap*; suicid* AND pharma* AND scale; antisuicidal AND pharma*. These searches were limited to peer-reviewed journal articles and reviews in the English language. Randomised, controlled trials (RCT) prospectively designed to measure reduction in suicidality/suicidal behaviors as a result of pharmacotherapy were investigated for this review, and due to the ethical problems of double-blinding such studies, open-label randomized, controlled studies meeting the other inclusion criteria were also included. References of relevant articles were also investigated for additional papers.

Results

Combining the six searches resulted in 953 abstracts for consideration after excluding duplicates. Once abstracts not presenting interventions in prospective studies designed to measure effects of pharmacotherapies on suicidality were excluded, 7 studies were left to be synthesised.

Mood stabilisers – lithium

An RCT comparing potential anti-suicidal effects of ***lithium*** to placebo for 12 months in depressed patients who had recently attempted suicide found no statistical difference between those treated with placebo and those with lithium, however all suicides occurred in the placebo group[4]. The study failed to reach prospectively calculated numbers needed to show effect for both comparison groups (lithium and placebo), however a post hoc analysis of completed suicides that all occurred in the placebo group showed an adjusted hazard ratio of 0.517 (NS) in the survival analysis, suggesting an anti-suicidal effect for lithium. Another, more recent 2.5-year double-blind RCT comparing ***lithium*** to sodium valproate in the time to suicidal events (suicide attempt or suicide ideation with a plan, requiring change in treatment) in 94 persons with bipolar disorder and at least one previous suicide attempt[5]. This trial failed to find a difference between the treatment groups, and the authors suggested estimates of relative risk of suicide for lithium vs. other treatments from earlier meta-analyses of previous studies may be too high. An older, open-label RCT prospectively investigated the occurrence of suicide attempts and completions over 2.5 years in two pharmacotherapy comparisons[6]. ***Lithium*** was compared to amitriptyline/other drug in 93 patients with major depression, and to carbamazepine in 175 bipolar patients and 110 schizoaffective patients. There were no suicide attempts or completions among those taking lithium, while in the carbamazepine group there were 5 attempts and 4 completed suicides, and 5 completed suicides in the other medication group.

Atypical antipsychotics

A 2-year open-label randomised trial comparing olanzapine and clozapine in 956 patients with schizophrenia or schizoaffective disorder, and considered to be at high risk of suicide, found that patients taking ***clozapine*** had lower rates of suicide attempts and completions, and less urgent suicide preventative interventions needed during the trial than those taking olanzapine[7]. The positive impact of clozapine appeared to be due to its own effects rather than those of concomitant other psychotropic medications[8]. The trial was designed as an open-label study with masked ratings so that possible suicidal crisis could be intervened with rapidly, and so that necessary procedures with the use of clozapine (regular blood tests to detect possibly developing agranulocytosis) could be performed without risking patient safety[7].

Typical antipsychotics

Flupenthixol given as depot injections was found to significantly reduce the number of suicide attempts compared to placebo after 4 months and for the remainder of a 6-month randomized, controlled study of patients with personality disorders, mainly borderline personality disorder[9].

Antidepressants - Selective serotonin reuptake inhibitors (SSRI)

Paroxetine was compared to placebo in a 1-year double-blind RCT of 91 patients with at least one previous suicide attempts, and not diagnosed with major affective or psychotic disorder, organic mental disorder, or substance abuse disorder[10]. When adjusting for previous suicide attempts, paroxetine reduced the recurrence of suicide attempts significantly. A recent pilot-scale prospective RCT comparing ***paroxetine*** (SSRI) to bupropion (a noradrenaline-dopamine reuptake inhibitor, NDRI) effects on suicidal behaviours in a sample of persons considered at high risk of suicide and with major depressive disorder found that paroxetine appeared to offer more relief from symptoms[11]. The authors believed this may have been due to paroxetine effect on serotonergic transmission, whereas bupropion is believed to have no such effects. Relief from suicidal ideation was greater in patients with more severe initial suicidality scores.

Noradrenergic and specific serotonergic antidepressant (NaSSA)

Mianserin was compared to placebo in a 6-month randomized, controlled study of 38 persons with a personality disorder and a history of a suicidal act causing hospitalisation before recruitment, and no differences were observed between groups[9]. There were fewer suicides in the mianserin group compared to the placebo group, but the difference was not statistically significant.

Conclusions

Despite decades of research and clinical use of many psychotropic medications in patients who are experiencing acute or chronic suicidality, solid evidence of their effectiveness in reducing suicidal behaviours is very scarce. It can therefore be argued that we need more research to develop better pharmacotherapies. Numerous investigators have called for more such studies over the years, but perhaps due to the inherent problems in having persons at high risk of suicide in randomised patient groups, or in double-blinded designs, such studies do not exist. Risk-management may be difficult, however improving study participant monitoring, and using other study endpoints than completed suicide, such as suicide ideation or suicide attempts can reduce risks by enabling emergency interventions when needed and make studies more ethically acceptable[5]. However, concerns have been raised about the comparability of close monitoring to “real life” care settings[12]. Study designs should also look at suicidality specifically and prospectively to obtain reliable results, and not just rely on one or two items on a depression scale but rather use a suicidality scale[13]. RCT study designs should be used to improve reliability, but most such studies are of relatively short duration only, complicating comparability to “real life” again, and also the statistically rare event of suicide may not occur in such short time frames[14]. Selection bias may also confound results, as suicidal patients are often excluded from clinical trials of new pharmaceuticals. The massive costs involved in running RCTs limit agencies capable of performing such studies, possibly biasing studies through using commercial funding bodies.

In summary, we have very limited evidence to justify using current pharmacotherapies for treatment of suicidality. Much of our knowledge relies only on a few studies, and applicability to different patient groups and settings may not be straightforward. Clinicians can and must use their best judgment and experience and tailor treatments to their clients, but in order to develop more effective therapies, more research is still desperately needed.

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