
ANTIDEPRESSANTS AND SUICIDE

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Antidepressants can be helpful in preventing the suicide of a depressed person in clinical practice, but there is also a discussion about whether antidepressants can raise the risk of suicide in certain situations.

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Contents

Introduction	3
Causation	3
Children and Adolescents	4
Children.....	4
Adolescents.....	4
Are all Antidepressants Equal?	4
Non-SSRIs.....	5
Inclusion Criteria	5
Motivation	5
Reasons.....	6
Research Problems	6
Confounding	6
Sponsored Studies	7
Age	7
Risk-Benefit Ratio.....	7
Monitoring	8
A Better Understanding.....	8
References	10

Introduction

Prescribing of antidepressants has increased greatly over the last decades. This increase has coincided with a fall in rates of suicide, leading some researchers to suggest a causal association. As depression is the main psychiatric condition leading to suicide, it seems reasonable to infer that rises in antidepressant prescribing, which indicate improved management of depression, should have a beneficial effect on suicide rates. Indeed, an intervention to improve general practitioners' management of depression in a Swedish community resulted in increased antidepressant prescribing and a short-term reduction in suicide. However, one also needs to bear in mind that the effectiveness of antidepressants in childhood and adolescence is less clear than in adults.

However, there is a concern that antidepressants may precipitate suicidal behavior. In October 2004, the US Food and Drug Administration issued an advisory that antidepressants may be associated with an increased risk of suicidal thoughts and behaviors in children and adolescents. These warnings were prompted by a meta-analysis of all available randomized trials of antidepressants in this age group, in which patients randomized to antidepressants had nearly twice the rate of suicidal ideation or behavior relative to those given placebo. These concerns prompted the US Food and Drug Administration to undertake a reanalysis of all its available antidepressant trials in adults as well. This meta-analysis and several subsequent analyses of short-term trials found no increased risk of suicidality in adult antidepressant users. However, the situation seems to be different for children and possibly adolescents.

Causation

Despite the widespread use of antidepressant medications, particularly selective serotonin reuptake inhibitors (SSRIs), there is inconsistent evidence that growth in antidepressant use has reduced the prevalence of suicidal ideation or suicide attempts during the past decades. (Haverkampf, 2018a) Nonrandomized studies comparing users of different antidepressant classes, including SSRIs, tricyclic agents (TCAs), serotonin-norepinephrine reuptake inhibitors and other drugs, have reported small or no differences in suicides and suicide attempts. However, serious questions remain whether these studies had adequate statistical power or were adequately controlled for prescribing biases caused by preferential avoidance of TCAs in patients at high risk. Since suicidal thoughts and behaviors do not happen in a vacuum, there are many aspects most studies on suicidal behavior may not account for, which can, however, be highly relevant. Internal and external communication seems to play a more fundamental role in suicidal ideation, which is also affected by medication, but not solely by it.

Children and Adolescents

An increased risk of suicidal behavior has been reported in children and adolescents. It is possible that an increased short-term risk may be counterbalanced by a longer-term reduction in suicidal behavior. Another explanation given has been that patients on SSRIs may be more open about how they feel.

Time trends for suicide and non-fatal self-harm in children and adolescents have not provided consistent evidence of adverse trends paralleling increased prescribing in the 1990s, although there is some evidence of a rise in non-fatal self-harm in young females. Furthermore, in the United States, research suggests that patients in their teens, the age group with the largest increase in antidepressant use, experienced the greatest falls in suicide.

Children

There is no strong evidence that increases in antidepressant prescribing lie behind recent reductions in population suicides. Furthermore, data from pediatric trials suggest that SSRIs are associated with an increased risk of suicidal behavior and most SSRIs seem to be ineffective for childhood depression. However, current concerns about the safety of SSRIs come from clinical trials both of too short duration (< 10 weeks) to identify longer term beneficial effects and are carried out in children and adolescents, among whom suicide is rare.

Adolescents

A US Food and Drug Administration advisory has warned that antidepressants may be associated with an increased risk of suicidal thoughts and behaviors in adolescents. This prompted a meta-analysis of trials in adults that found no overall increase in risk, but individual agents could not be studied. A later study concluded that there were equal event rates across antidepressant agents. A review of evidence from pediatric trials by the Committee on Safety of Medicines in Britain led to most selective serotonin re-uptake inhibitors (SSRIs) being contraindicated in patients younger than eighteen.

Are all Antidepressants Equal?

There has been the theory that the less activating antidepressants, that is the SSRIs rather than the SNRIs, may be a safer choice if there is a risk of activating suicidal thoughts. However, there is not much empirical data to support this.

Several observational studies have reported small or no differences in suicides and suicide attempts between antidepressant classes and a meta-analysis of randomized controlled trial data that found no difference in suicide attempt rates between SSRI and TCA users. Similar to a cohort study using General Practice Research Database data, they found a higher rate of suicidal acts in venlafaxine users compared with SSRI users, even

after adjustment for measured confounders. This effect was attenuated in secondary analyses restricted to treatment-naïve users, suggesting some residual confounding in our primary analysis. In contrast to a case-control study in Ontario residents aged 66 years and older, they did not observe an increased risk of violent suicide among SSRI initiators relative to initiators of other antidepressants.

Non-SSRIs

A nested case-control study in residents of Ontario, Canada, aged 66 years and older found that SSRIs were associated with a nearly 5-fold increased risk of suicide during the first month of treatment compared with other antidepressants, but it found no difference between classes during subsequent periods. The investigators also observed a higher risk of violent suicide among SSRI users. However, a study using postmortem data found that a lower proportion of suicides was violent among SSRI users than among non-antidepressant users.

Inclusion Criteria

The inclusion criteria and the factors controlled for seem to play an important role. For example, studies have documented that venlafaxine tends to be prescribed to people with past SSRI treatment failure and with a greater burden of suicide risk factors, which needs to be controlled for. In one study, the differences between citalopram and fluoxetine were attenuated when the population was restricted to subjects with no antidepressant use in the 3 years prior to antidepressant initiation. In the same study, the higher risk of venlafaxine was attenuated when the population was restricted to subjects with no antidepressant use in the 3 years prior to antidepressant initiation. However, citalopram was linked less to violent suicide attempts, even when restricting treatment to treatment-naïve subjects and no suicide attempts for the previous three years.

In a study of a population of 287 543 adults aged 18 years and older initiating antidepressant therapy in British Columbia between January 1, 1997, and December 31, 2005, the researchers observed no clinically meaningful variation in the risk of suicide and suicide attempt by the type of antidepressant initiated. Effect sizes became more similar after restriction to subjects without any antidepressant use in the past 3 years, a population which is probably much closer to a population of first-time antidepressant users and an analysis within this population is less confounded by prior treatment experience and progression of the underlying condition, providing a more valid estimate of the causal treatment effects.

Motivation

Suicide is rare, even among people with depression. Thus, most clinical trials have insufficient power to provide clear evidence on the effect of antidepressants on suicide. Since suicidal ideation and behavior is multifactorial looking only at a possible direct effect of the antidepressant rather than at how this effect may interact with other factors and their effects can be misleading. Besides psychological intrapersonal factors and the effect of

a different mood on interpersonal communication, external factors, such as the available means to commit suicide can play a role.

Since motivation is a product of applying one's internal basic parameters, such as needs, values and aspirations to the world, it requires the ability to read this information. If survival as a need and continued life as a value and aspiration are very basic to our existence, a motivation to commit suicide must mean that information is either not read or read incorrectly. Most mental health conditions have an effect of internal communication patterns (Haverkamp, 2010b, 2010a, 2017a, 2018b), which can also change the information which is available about oneself. By ameliorating the condition and its effects, antidepressant medication can so also prevent suicidal ideation and behavior.

Reasons

An important question which is often left unanswered is why an individual commits suicide, this ultimate aggressive act turned against oneself. Medication can lower certain symptoms of depression but it cannot directly address a complex thought process. (Haverkamp, 2010a, 2018d, 2018c) Many different factors should to be addressed in therapy, but paramount about them is how a person communicates with himself or herself and with others. Distortions in communication systems are quite often a reason that leads to misperceptions, misattributions and unhelpful thought patterns.

Research Problems

Most population studies have concluded that recent rises in prescribing have contributed to falls in suicides, although there are exceptions. Interpretation of the findings is not straightforward. As mentioned above, several factors usually need to fall in place that an individual contemplates suicide. Also, a range of factors can influence population suicide rates. It is therefore challenging to distinguish the discrete effects of increased antidepressant prescribing from changes in other risk factors.

Confounding

Confounding occurs if, for example, certain antidepressants were more likely to be given to patients with a greater background risk of suicide. This makes it necessary to control for sociodemographic, clinical, and health care utilization factors likely to be independent predictors of suicidality using traditional multivariate and high-dimensional propensity score techniques. The ability to fully adjust for mental health status is frequently limited by the measurement and reporting of mental health conditions as ICD-10 diagnoses.

Well-validated behavioral risk factors such as impulsivity and hopelessness, environmental factors such as access to lethal means, and family history of completed suicide would not be measured in claims data. Random

misclassification of confounders in health care utilization databases leads to incomplete adjustment of confounding bias.

While underreporting of suicide deaths is likely nondifferential, there is a possibility that patients treated with specific agents or having specific histories might attract closer scrutiny for potential suicide. Patients using TCAs, which are known to be fatal in overdose, might be more likely to receive a suicide diagnosis.

Sponsored Studies

Soon after the launch of fluoxetine a series of reports were published suggesting worsening of depression and emergence of suicidal thoughts in some people. The discussion became more heated after a review of data from pediatric trials of SSRIs suggested that published findings present a more favorable risk-benefit profile than unpublished trials sponsored by industry. It is true that many studies in this area have been supported by the pharmaceutical industry, which in itself is not necessarily bad, but it has probably contributed to the intensity of the discussion.

Age

Furthermore, declining overall suicide trends may mask rises in some age and sex groups. In Australia, rises in antidepressant prescribing were associated with falls in suicide among some age and sex groups but increases in others.

There are two reasons why an adverse effect of antidepressants on suicide risk may have been overlooked in adult clinical trials. Self-harm is fortunately still relatively rare, and most clinical trials lack power to detect any increased risk. Also, the possibility may not have been specifically investigated in the clinical trials. The increased risk in children may have been detected either because of the increased prevalence of suicidal thoughts and self-harm in young people (giving greater power) or because the absence of beneficial effects meant that adverse effects dominated the clinical picture.

Risk-Benefit Ratio

From the population perspective, the balance sheet of risks and benefits of SSRIs is unclear. Any antidepressant induced suicides are probably offset by the beneficial effects of antidepressants on depression and long-term suicide risk associated with untreated depression. The low toxicity of SSRIs in overdose will have prevented

some suicides. The balance of risks and benefits may vary depending on an individual's underlying suicide risk. For patients with conditions that have a high risk of suicide, such as severe depression, the risk-benefit balance may be more favorable than for patients with conditions such as anxiety and mild depression, in which suicide is rare. It is in these lower risk conditions, however, that much of the recent rise in prescribing has probably occurred.

Depression is a common and disabling condition, and so the safety of drugs used in its management is crucial. Future trials of antidepressants should be of sufficient duration to detect longer term benefits of this class of drug and balance these against possible risks. They should also systematically collect data on suicidal thoughts and behavior. Long term studies are required to assess the effect on population health of recent rises in antidepressant prescribing.

Monitoring

Treatment decisions should be based on efficacy, and clinicians should be vigilant in monitoring after initiating therapy with any antidepressant agent. SSRIs are often the preferred choice in adults. Overdoses of antidepressants are still a common means of suicide because of their availability to the patient. Tricyclic antidepressants are considerably more toxic in overdose than SSRIs. Consequently, a switch from tricyclics to SSRIs as first line treatment for depression could prevent a significant number of overdose deaths a year. However, medication switches seem rare in clinical practice. As the rate of antidepressant prescribing has increased in general, the prescribing of SSRIs has increased, but the number of patients on TCAs has not decreased by much.

A Better Understanding

However, equally important is to understand why suicides occur. The motivation behind a suicide may be due to a mix of several factors. As mentioned, CFT works with internal and external communication patterns to work out individual needs, values and aspirations in the short and long run, while paying attention to any concurrent psychiatric conditions. It is important to realize that suicidal thinking and behavior is usually not solely due to changes in mood or other psychiatric parameters. (Haverkamp, 2012a, 2012b, 2017b)



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