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### Abstract

*Based on a 10-year systematic review of suicide prevention strategies, 29 suicide prevention experts from 17 European countries recommend four allegedly evidence-based strategies to be included in national suicide prevention programs. One of the recommended strategies is pharmacological treatment of depression. This recommendation is problematic for several reasons. First, it is based on a biased selection and interpretation of available evidence. Second, the authors have failed to take into consideration the widespread corruption in the research on antidepressants. Third, the many and serious side effects of antidepressants are not considered. Thus, the recommendation may have deleterious consequences for countless numbers of people, and, in fact, contribute to an increase in the suicide rate rather than a decrease.*

### Problematic advice from suicide prevention experts

In the paper, *Evidence-based national suicide prevention taskforce in Europe: A consensus position paper*, “29 suicide prevention experts from 17 European countries” (Zalsman et al. 2017, p. 419) list four allegedly evidence-based strategies that should be included in national suicide prevention programs: (a) Restriction of access to lethal means, (b) treatment of depression (pharmacotherapy and psychotherapy), (c) ensuring chain of care, and (d) school-based universal prevention (Zalsman et al., 2017). These strategies are based on a 10-year systematic review of suicide prevention strategies conducted by “18 suicide prevention experts” (Zalsman et al., 2016), 15 of which overlap with the experts authoring the consensus position paper. Together, the terms *evidence-based*, *consensus*, and *suicide prevention experts* convey an authoritative message others are likely to follow and governments to fund. In this paper, we demonstrate that the authors make a number of problematic assumptions with regard to the view that pharmacological treatment of depression should be included in national suicide prevention strategies.

### **The review constituting the evidence base is biased**

Zalsman et al.’s (2016) review is biased in that it does not include the numerous studies or reviews not supporting the authors’ recommendation. For instance, ecological studies that have found an inverse correlation between use of antidepressants and the suicide rate are included (Gusmao et al., 2013). Ecological studies finding no such relationship are excluded (Zahl, De Leo, Ekeberg, Hjelmeland & Dieserud, 2010). Moreover, Zahl et al. (2010) showed that some of the studies claiming to have found that increased sales of antidepressants was associated with a decrease in the suicide rate were flawed. Most importantly, however, is that ecological studies cannot say anything about causal effects and

can therefore not constitute any *valid* evidence base for recommending use of antidepressants to prevent suicide.

Randomized controlled trials (RCTs) are normally considered gold standard studies with regard to demonstrating treatment effects of medications, and the review by Zalsman et al. (2016) includes some RCTs and reviews of the same. Again, the review seems selective. For instance, it does not include Fergusson et al.'s (2005) systematic review of 702 RCTs finding that the rate of attempted suicide increased more than twofold in patients receiving selective serotonin reuptake inhibitors (SSRIs) compared with placebo or other treatments. Fergusson et al. (2005) also point out several methodological problems with the published trials (discussed further below).

What is also missing from the Zalsman et al. (2016) review is the meta-analysis conducted by the US Food and Drug Administration (FDA; Stone et al. 2009). This review found the risk of suicidality associated with the use of antidepressants to be highly age-dependent. There was an increased risk for suicidality among adults under 25; no effect for the age group 25-64; and a reduced suicide risk in those aged 65 years and over. This study has later come under scrutiny. According to Gøtzsche (2015), the FDA actually found increased risk of suicidal behaviour for those up to 40 years of age but decided to split age groups differently when publishing the data to make it appear as if the increased risk was for young people only.

With regard to children and adolescents, Högberg, Antonuccio and Healy (2015) showed that the risk for suicidal behaviour in the *Treatment of Adolescents with Depression Study* (TADS) was higher than it first appeared among the adolescents treated with antidepressants compared to the placebo group. Healy (2007), in a paper pertinently titled *One flew over the conflict of interest nest*, maintained that “the greatest known divide in medicine between the raw data on an issue on the one side and the published accounts

purporting to represent those data on the other” (Healy, 2007, p. 26), concerns paediatric trials on SSRIs. Published and unpublished data taken together indicate that SSRIs do not work and are also hazardous (Healy, 2007). Still, Zalsman et al. (2016) maintain, “In children and adolescents with depression, evidence does not support avoidance of use of antidepressant medication because of increased risk of suicidal behaviour.”

### **Problems related to RCTs on antidepressants are not considered**

There are several problems connected to RCTs and the effect of antidepressants on suicidality. Some are methodological in nature, for instance, non-effective blinding of trials. Since antidepressants have conspicuous side effects, patients and doctors will know whether the drug is an antidepressant or a placebo (Gøtzsche, 2015). Others are tied to widespread corruption (Gøtzsche, 2015). Sometimes the two sets of problems are intertwined. Zalsman et al. (2017) fail to take into consideration the well-documented fact that pharmaceutical companies and their allies in psychiatry have contributed to a publication bias in favour of antidepressants with regard to suicide (Gøtzsche, 2013; Gøtzsche, 2015; Healy, 2008). In a landmark study of 74 FDA-registered RCTs, Turner, Matthews, Linardatos, Tell and Rosenthal (2008) showed that, with very few exceptions, RCTs finding negative or questionable effects of antidepressants were either not published, or published in a way that made the outcome seem positive. All but one study finding positive effects were published.

Gøtzsche (2015) argues that fraud more broadly, and unethical practices in particular, contribute to the underestimation of suicidal risk in RCTs. What follows is his summary of these problems: Some of these practices include researchers not reporting suicide attempts during trials. When attempts are reported, they are coded as something else (e.g. an overdose). Furthermore, companies often include people with very low risk of suicide. Sometimes trials have initial periods with participants on active medication and then exclude

participants displaying pronounced side effects before the actual trial. Sometimes participants are on antidepressant treatment before they are randomized, which then leads to withdrawal symptoms (due to cold turkey termination of the antidepressant) in the placebo group that, in turn, increases the risk of suicide. Thus, the difference between the groups with regard to suicide is minimized. Companies sometimes also encourage researchers to prescribe benzodiazepines in addition to the antidepressant to avoid some of the more pronounced side effects. Still further, suicidal behaviour shortly after the active treatment is not recorded. Participants may be followed closely in the trials, but the antidepressant may be terminated before a serious problem develops. In clinical practice, it is not possible to follow the patients so closely, and they can forget to take their medicine. This may, in turn, increase the risk of suicide due to withdrawal symptoms (Gøtzsche, 2015).

Healy (2006) has shown how both the FDA and pharmaceutical companies have manipulated data and its statistical analyses to get the results they wanted. One clear example is *Study 329*. This was a double-blind RCT study to evaluate the efficacy and safety of an SSRI (paroxetine) for adolescents with major depression. Funded by GlaxoSmithKline (GSK), this study was, according to Healy (2008), largely ghost-written. The reported results indicated that paroxetine was effective and safe (Keller et al., 2001). It was later revealed that in 1998, GSK already had concluded that the drug in question did not work, but that “positive” aspects should be selected for publication (Healy, 2008). Under the “restoring invisible and abandoned trials” (RIAT) initiative, *Study 329* was recently reanalysed with the results now showing that paroxetine was not effective for major depression and that the drug actually had a number of serious adverse effects, including those related to suicide (Le Noury et al., 2015).

Gøtzsche (2013, 2015) also documents that on several occasions the FDA protected pharmaceutical companies rather than the participants in the RCTs. Based on his calculations

of published and unpublished data, he maintains that the actual number of suicides connected to the use of antidepressants probably are 15 times higher than what was reported by the FDA, all of which amounts to an error of 1.400% (Gøtzsche, 2015). Based on this massive underreporting of suicide, he concludes that SSRIs most likely increase the prevalence of suicide in all ages (Gøtzsche, 2015).

### **Harmful side effects are not considered**

Zalsman et al. (2017) also fail to consider the serious consequences in terms of harmful side effects of antidepressants. Among others, Gøtzsche (2015) has extensively documented how a corrupt pharmaceutical industry has systematically denied or toned down harmful side effects of antidepressants (e.g. *Study 329*). In their systematic review of published versus unpublished data on SSRIs, Whittington et al. (2004) found that whereas the published data suggested a favourable risk-benefit profile, the addition of unpublished data indicated that the risks could outweigh the benefits in the treatment of depression in children and adolescents.

In their review of antidepressant studies, Antonuccio and Healy (2012) conclude that so-called antidepressants: 1) are not more effective than placebo in relieving depression for the vast majority of people who take them, 2) do not offer a risk/benefit balance exceeding that of alternatives, 3) may increase suicidality, 4) increase anxiety and agitation, 5) interfere with sexual functioning, and, 6) increase depression chronicity. Based on all this, they argue that antidepressants do not even justify their label since many of the side effects actually have larger effect sizes in studies than do the antidepressants. Thus, according to Antonuccio and Healy (2012), they could just as well be called antiaphrodisiacs because of the very common negative effects on libido and sexual functioning.

In a more recent review and meta-analysis of clinical study reports, Sharma, Guski, Freund, and Gøtzsche (2016) revealed discrepancies in reporting, which may have led to a serious underreporting of harmful side effects. Still, they found that the risk of suicidality and aggression doubled for children and adolescents who took antidepressants in comparison to the placebo group. Given that these side effects are commonly known, it is particularly strange that Zalsman et al. (2017) did not account for them. Alongside suicidality, some of the side effects include: violent behaviour (including murder); making a depressive episode chronic that otherwise would most likely have passed by itself; psychosis; anxiety; agitation; akathisia; sexual dysfunction; hostility; loss of emotion; lethargy; not feeling like oneself; loss of creativity; nausea; headaches; sweating; dizziness; confusion; cramps; memory loss; sleeping problems; and dependency of medication (Antonuccio & Healy, 2012; Gøtzsche, 2015). This begs the following question: if antidepressants do in fact produce all these side effects detrimental to the well-being of a person, will their prescription actually increase suicidality?

### **The basis for the experts' recommendation is flawed**

The basis for Zalsman et al.'s (2017) recommendation is the assumption that suicide is caused by, or a consequence of mental disorder, mainly depression. The belief is that if we treat the depression, the person will no longer be suicidal. Unfortunately, this is not necessarily the case. First, the so-called evidence-base for the strong connection between mental disorder and suicide, with its inherent causal implications, is weak (Hjelmeland, Dieserud, Dyregrov, Knizek, & Leenaars, 2012). It mainly consists of findings from psychological autopsies that are fraught with methodological problems, particularly with regard to the diagnostic process. Hence, it cannot constitute any *valid* evidence-base for the often-cited 90 per cent statistic, namely that at least 90 per cent of suicides are related to a



mental disorder (Hjelmeland et al., 2012). Second, as qualitative suicide research has burgeoned, the strong association between mental disorder and suicide has come under further scrutiny. Qualitative studies contextualizing suicide indicate that suicide is more connected to existential and contextual issues than to mental disorder (Hjelmeland & Knizek, 2016; White, Marsh, Kral, & Morris, 2016). Medicalizing existential problems or contextual issues is highly problematic.

### **The consensus claim is misleading**

To make a statement regarding consensus might simply mean that a group of people has agreed on something without any further implications. However, when consensus is mentioned in connection with “evidence based strategies for suicide prevention”, recommended by “suicide prevention experts” (29 of them, with some holding influential positions), we expect quite a few readers will interpret this to mean that the suicide prevention expert community has agreed on what is best to do to prevent suicide.

To give the impression that there is consensus in the field of suicide prevention is very misleading. Due to suicide’s complexity, there is not, and probably never will be, consensus in the field of suicidology. Arguably, consensus may very well be uncalled for, or not desirable if it means producing a “one-size fits all”-strategy of suicide prevention. There is far too much variety with regard to individual as well as contextual factors connected to suicidality (Hjelmeland & Knizek, 2016). Instead of being seen as a weakness, disagreements between professionals working in the field of suicide prevention should be considered a strength and embraced as a basis for fruitful discussions for the purpose of responding to suicide more effectively and moving forward the field of suicidology. Unfortunately, voices critical of mainstream versions of suicidology are often unwelcome by influential professionals such as researchers in leading positions and journal editors (Healy, 2008;

Hjelmeland & Knizek, 2017; Kirsch, 2008). This hinders not only the maintenance of open debates, but also the development of the field of suicidology, where publications repeatedly do nothing more than repeat the status quo (Hjelmeland, 2016).

### **Conclusion**

Most antidepressants are prescribed by general practitioners (GPs), often without noting a psychiatric diagnosis, which means they are often prescribed not for a formal diagnosis of depression, but for symptoms of depression only (Mojtabai & Olfson, 2011). GPs may or may not at the same time refer the patient to psychological treatment. Either way, waiting lists for psychologists are normally quite long, or, as is the case in many low and middle-income countries, psychologists may virtually be inaccessible. Besides, prescription of antidepressants appears much cheaper and is therefore likely to be embraced by patients as well as governments as the first, and probably often the only choice.

If antidepressants indeed have little effect on depression and/or suicidality, but a number of serious side effects, some of which actually may increase the risk of suicide (Antonuccio & Healy, 2012; Gøtzsche, 2015; Sharma et al., 2016; Whittington et al., 2004), Zalsman et al.'s (2017) recommendation is not supported. It is not evidence-based; it is based on a biased selection and interpretation of available evidence. Moreover, the authors have failed to take into consideration the widespread corruption in the research on antidepressants, as well as the many and serious side effects of SSRIs. Without reservation, they recommend pharmacological treatment of depression as one of the four "evidence-based strategies" that should be included in national suicide prevention programs. This may have deleterious consequences for countless numbers of people, and, in fact, contribute to an increase in the suicide rate rather than a decrease.

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