

From the Serotonin Model of Suicide to a Mental Pain Model of Suicide

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This is the story of a journey in suicide research. After 20 years, it may be time to abandon [1] the initial hypothesis (serotonin) and propose a unifying hypothesis for an extremely complex human behavior called suicide behavior (SB). This unifying hypothesis (mental pain) is new in the authors' articles but has been described in the literature for more than 20 years [2, 3].

A Story with a Wrong Beginning: The Serotonin Model of SB

This story started in the 1990s when optimism about the future of the biological approach in psychiatry in the late 20th century was at its peak [4]. Clinical psychiatrists approached suicide fundamentally as a medical issue; a textbook stated that '95% of suicides had a diagnosable psychiatric disorder' [5]. Research psychiatrists approached it using the serotonin model of suicide [6] and the associated clinical model based on a small sample of patients with depression [7]. Contributions criticizing the serotonin model had to be published in nonmainstream journals [8, 9].

After the first article on suicide attempts [10], the first author, influenced by the prevailing environment, advised his young mentee (the second author) that he needed to focus on biological factors, such as hormones and genes in the context of the serotonin model of SB, and on suicide attempters, who were much easier to study in a clinical setting than suicide completers.

A Crucial Turning Point

Instead of describing how we published many articles after progressively recruiting larger clinical samples of suicide attempters, we want to emphasize a very unsuccessful article which, after repeated attempts, was finally published in a journal not listed in PubMed [11].

To understand this article, some basic statistical concepts are needed. All psychiatrists know that, to publish a study, you need to obtain a 'statistically significant' value with a $p < 0.05$. Most psychiatrists do not know that this is an arbitrary convention established by statisticians long ago, and that other statistical concepts are more important in scientific research. The 'effect size' [12] is much

more important than significance for understanding the relevance of variables in clinical settings; it measures how 'large' or 'small' the effect of a studied variable is. Without detailing the statistical problems with odds ratios (ORs) [13], most statisticians would probably agree that in a case-control study with a dichotomous dependent variable (e.g. SB or no SB) the OR is the recommended statistical method for measuring the effect size. The OR calculates the effect size of the association of SB with an independent variable (e.g. female sex) in a univariate cross-tabulation analysis (the χ^2 test provides the p value). Logistic regression can then be used to adjust the OR for the effects of other confounding variables, such as age.

To summarize, in many articles we used ORs to measure the effect sizes of variables in SB using case-control designs. The unsuccessful article [11] focused on the effects of life events and personality traits in a sample of >500 subjects (>200 cases and >300 controls). The findings were not new; life events and personality traits had huge effects, with an OR >10 when comparing SB cases with controls. What was new, and probably annoyed the reviewers from mainstream psychiatric journals, was our acknowledgment that in prior articles on SB the effect of biological measures, such as hormones and genes, was associated with lower ORs, which merely ranged from 1–2, while psychosocial factors appear to have ORs >10 [11].

The Third Man

Anyone familiar with movies would guess that a third man could only mean trouble. When the third author arrived to help the second author, the third man decided to pursue analysis to verify and clarify how life events and personality traits contribute to SB [14]. Then he proposed that, rather than biological or genetic variables, life stressors may be the best way to identify psychiatric patients at risk of suicide [15].

Starting to Ask Painful Questions: What Is SB?

A sophisticated reader may ask us to define SB. As a matter of fact, to get our articles published in scientific journals, we used a standard definition of suicide attempts [16]. Regarding SB, any clinician would probably agree that there are three major levels of SB: suicidal ideation, suicide attempt, and completed suicide [16].

Before moving on to the research problems of these three levels of SB, two painful acknowledgments need to

be made. Our suicide research has been completed in Western countries, so our experience may have little relevance for SB in non-Western countries. Like others, when reviewing worldwide data [17], we found that completed suicide in developing or non-Western countries may be a different phenomenon because there 'socioeconomic and cultural factors appear to play a major contributing role in suicide' [17]. To be precise, our experience may apply only to Western countries in contemporary times; socioeconomic and cultural factors probably were more important in Western countries during the 19th century, as the French sociologist Durkheim [18] postulated [19].

The second acknowledgement is that any comments on the relationships between the frequencies of suicidal ideation, suicide attempts, and completed suicide are limited because there is no systematic research in Western countries using the same population to study frequencies of suicidal ideation, attempts, and completed suicide. Rates need to be estimated by forming a complex puzzle of multiple studies from multiple countries with multiple designs to try to provide a coherent understanding of SBs in Western countries [20].

The prevalence of suicidal ideation in Western countries ranges from 2 to 14% [21] but, as most of the people who report suicidal ideation do not attempt suicide [22], suicidal ideation must be essentially a different phenomenon from suicide attempts. Adding a 'wish to die' may increase the specificity of suicidal ideation [23]. Suicide attempts in Western countries are a reasonably good research target compared to completed suicide since attempters: (1) have a sufficient frequency (i.e. around 1–2% of the population [21] vs. an annual incidence of completed suicide measured per 10,000 individuals with values around 1 per 1,000 [24]) and (2) can be studied in hospitals versus using mortality samples. Thus, we, like most suicide researchers, study suicide attempters and try to extrapolate from them to suicide completers. However, from the statistical point of view, two major problems may exist when using this research strategy. They can be explained using two overlapping concepts: (1) suicide completers may be outliers within the group of suicide attempters, and (2) suicide attempters and completers may be different populations with relatively little overlap.

The concept of outliers is a complex statistical concept not easy to define [25] and refers to 'extreme' subjects not well represented by typical statistical measures such as the mean (a measure of central indexes); the outliers are the subjects in the 'tail areas' of the distribution [25]. Outliers are a major problem for approaches derived from evi-

dence-based medicine (EBM); EBM resolves the problem by ignoring the outliers and focusing on the mean [26]. Heterogeneity, another possibly important issue in SB, is also a problem in EBM approaches [26–28].

A major statistical problem is created by assuming that the annual incidence of completed suicide in Western countries is approximately 0.02% [20] (or 20 per 100,000/year) and that the prevalence of people reporting prior suicide attempts in cross-sectional surveys is approximately 2% [20]. The number of suicide completers is approximately 100 times lower than the number of attempters. This cannot be easily explained as a difference in prevalence (cross-section) versus incidence (annual rate). Completed suicide attempters are rare (probably outliers) within the attempter group. As a matter of fact, a meta-analysis estimated a 1% annual incidence of completed suicide after nonfatal self-harm acts, but this concept may be wider than suicide attempters and this estimation is limited by the study limitations [29].

There are few studies comparing attempters and completers within the same population, but the limited data available suggest that they may not even be the same population, since suicide attempts are mainly a psychiatric phenomenon. Attempters are patients frequently seen by psychiatrists, while the majority of completers are not seen by psychiatrists, although in approximately three fourths of the cases they may have been seen by primary care physicians [20]. As far as the authors can tell, attempters and completers are probably different but partly overlapping populations with some factors unique to completers [20, 30, 31]. A major methodological problem is that there are repeaters among suicide attempters. Some of them appear to be particularly prone to repetition [32, 33] and, therefore, can be ‘counted’ several times in studies of suicide attempters. Obviously, there are no repeaters among completers. Now it is time to explore the limits of the scientific approach in psychiatry [34].

Even More Painful Questions: The Problems of Scientific Methodology in Psychiatry

The previous section proposes that suicidal ideation, suicide attempts, and completed suicide may not be continuous phenomena and that those populations studied when researching ideation, attempts, or completed suicide may be different with some, but limited, overlap. These three levels may not operate like a continuous descent downhill but rather may function like three discontinuous steps. Particularly problematic from the statisti-

cal point of view is the hypothesis that most people with ideation do not attempt suicide; attempters, therefore, are ‘outliers’ within the group of people with suicidal ideation. This means that typical statistical designs/tests applied to people with suicidal ideation will not represent the attempters very well. Moreover, it would be catastrophic for the authors’ research, which applied typical statistical designs/tests used with suicide attempters, if the attempters did not represent the completers very well. In summary, what we conceptually call SB appears to be made up of heterogeneous groups of phenomena.

Psychiatry deals with hybrid objects [35]. Jaspers [36], 100 years ago, described psychiatry as a hybrid science since he proposed that psychiatrists must combine the methods of the natural sciences which ‘explain’ phenomena and the methods of the social sciences which help us to ‘understand’ phenomena [36, 37]. The concept of Pridmore et al. [38] of operationalized predicaments of suicide appears to be an initial reasonable approach combining causes (explanations) of and reasons (understanding) for suicidal acts. Psychological and social sciences may be very important in the study of suicidal ideation, which should be fundamentally understood rather than explained by biological ‘causes’. We found that psychosocial variables, such as life stressors interacting with personality traits (different stressors may have different meanings for different individuals), may be very important in studying suicide attempters [14, 15]. Biological variables may have little relevance as causes for suicide attempters. We think, but have no definitive data from the literature, that in Western countries biological variables such as genes may be much more important in completed suicide. When compared with attempters, suicide completers should probably include an overrepresentation of patients with bipolar disorder or severe cases of depression, which are probably intensely influenced by biological brain changes that may contribute to completed suicide.

In our studies two factors appear and reappear: completed/attempted suicide in the family and the use of alcohol during the attempt [39]. Due to the relatively low frequency ($\leq 10\%$) of familial suicide [39], our sample size was too small to explore two possible hypotheses (familial suicide is explained by shared genes or understood as a learned behavior). Similarly, we do not know if potential attempters use alcohol to disinhibit themselves and therefore attempt suicide or are people with no prior thought of suicide until they are intoxicated by alcohol. Our limited data [40] suggest that the latter is true; alcohol use may be more prominent in impulsive attempts with a low lethality.

If suicidal ideation, suicide attempts, and completed suicide are not continuous linear phenomena but are influenced at different levels by the relative weight of psychosocial versus biological predictors, it may make little sense to search for biomarkers of SB in general [41]. More thoughtful approaches to developing biomarkers are needed in psychiatry [42].

Human Bias and the Problem of Suicide Autopsies in Studying Completed Suicide

The previous section posited that biological variables may have something more to offer in explaining completed suicide, but it acknowledged the limited available proof. Another reasonable hypothesis is that completed suicide in Western countries is largely a heterogeneous phenomenon. Menninger [43] insisted on the individuality of each suicide. In some patients it may be a planned decision in the absence of an obvious mental illness but while facing life challenges. In others it may be driven by abnormal biological changes in the brain, such as in cases of bipolar depression or severe major depression.

Establishing the relative importance of psychosocial versus biological factors is not easy because completed suicides are studied in detail via psychological autopsies [44–46], a retrospective assessment that can easily be biased by researcher or family member beliefs. Psychological autopsy studies frequently provide data on agreement among the study researchers [43] but do not comment on researcher or family biases. It is natural to think that groups of researchers who believe that completed suicide is mainly driven by a biological illness would easily agree among themselves that most of their psychological autopsy cases are explained by some biological illness [46]. Because a psychological autopsy is a medical procedure, researchers who are prone to being biased in favor of psychosocial explanations for completed suicide are likely to be underrepresented in psychological autopsies.

Mental Pain as a Unifying Hypothesis for SB

Twenty years ago, instead of encouraging the second author to study the serotonin hypothesis [6], the first author should have encouraged him to read the classic article on mental pain by Shneidman [2] entitled ‘Suicide as Psychache’. The concept of mental pain goes back to Freud [47], and unbearable pain is central to the concepts

of Shneidman [2] and Orbach et al. [3] and the escape theory of Baumeister [48]. Later, attempts [3, 49–54] were made to define the concept of mental pain more specifically than Shneidman [2] had. Scales of mental pain have been developed [55–56] including the Psychache Scale [57], the Mental Pain Questionnaire [58], and the Psychological Pain Assessment Scale [59]. As a matter of fact, there is a large body of literature that provides empirical evidence for the relationship between mental/psychological pain and suicide [2, 3, 49–54].

The authors currently believe that mental pain is what unifies all SBs, and they have started to use measures reflecting mental pain which suggest that >90% of their patients with a suicide attempt report it [33].

Mental pain may be much more frequent in suicide attempts than the impulsive-aggressive behaviors associated with the serotonin model. If the hypothesis that suicidal ideation and probably many suicide attempts are better understood as mental pain than explained by biological causes, it is reasonable that these SBs would not be associated with any specific location in the brain or be conceptually amenable to brain imaging studies, since they may be secondary to other mental symptoms [37, 60]. Mental pain, on the other hand, may use the same brain mechanisms as other types of pain [61–63].

ORs and Population-Attributable Risk

In case-control studies, ORs can measure the effect size of associations at the level of the individual, but not at the level of the population. Let us assume that the death of a spouse is associated with an OR of 10.0 in a case-control study of suicide attempts. This effect would be small if only 5% of attempters had the death of a spouse as a stressor, but it would be much larger if 50% of the attempters presented this stressor. The population-attributable risk (PAR) [64], as opposed to ORs, measures the effect size at the level of the population. Imagine that you could totally eliminate the exposure to a factor associated with suicide; the PAR would describe how much suicide decreases in that population [64]. PAR, rather than OR, is the concept that makes sense whether you want to defend or argue against the hypothesis that depression explains 80–90% of completed suicides [65]. Few studies [66] of suicide attempts have tried to estimate the PAR because it requires access to the population from which the samples come.

Contemporary Western literature is limited and cannot be used to definitively demonstrate that biological

variables, or serious mental illnesses such as bipolar disorder and/or severe depression, may be relatively more essential to the mental pain leading to completed suicide than to the mental pain leading to attempted suicide. A recent comprehensive meta-analysis [67] of suicide in bipolar disorder, when focused on completed suicide, provided an OR of 2.9 for a first-degree family history of suicide, but only 14% (21/149) of the completed suicides had a familial suicide history, indicating a very low PAR for familial suicide as in our studies [39]. In a recent prospective study of suicide attempts in the US population, accumulation of psychopathology was the best predictor of suicide attempts [68]. Similarly, a comprehensive review [69] of mood disorders proposed that comorbidity contributes to suicide acts in mood disorders.

Li et al. [70] are very courageous and assumed that the EBM approach works well in the study of completed suicide worldwide and that completed suicide is not a heterogeneous phenomenon. They calculated relative risks (RRs; a concept parallel to ORs) and PARs using meta-analysis. The RR for any mental disorder was 7.5 (CI 6.2–9.0) for males and 11.7 (CI 9.7–14.1) for females, compared to RRs of 2.1 (CI 1.5–2.8) for males and 1.5 (1.2–1.9) for females in the lowest socioeconomic groups. As a lower socioeconomic level is much more frequent than mental illness, it is not surprising that their PARs were of a similar magnitude [70].

Need for Suicide Studies Focusing on PAR Associated with Mental Pain

The extensive literature [2, 3, 49–54] on mental pain in suicide and our experience that >90% of our patients with suicide attempts report mental pain [33] indicate that mental pain may be associated with a high PAR for attempted suicide, but that is less certain than the mental pain PAR for completed suicide. Review articles estimating PAR for mental pain in suicide attempts and completed suicide are needed. Assuming that mental pain may be present in the majority of suicide attempts and completed suicides, this may be what unifies all SBs. On the other hand, how mental pain can be explained or understood [36–38] probably varies across SB levels. In suicidal ideation, mental pain is probably mainly an expression of psychosocial issues and their meaning to that individual. In our case-control studies of suicide attempts, we found that small ORs (range 1–2) were associated with biological variables, while much larger ORs (>10) were associated with life stressors and per-

sonality traits [11], and that life stressors may have varying abilities to cause mental pain based on individual personality traits [14].

Conclusion

Recently, Healy [71] questioned the value of the serotonin hypothesis in depression. After 20 years of their own data serving as disconfirmation, it is time for the authors to abandon the serotonin hypothesis of suicide and clearly state that, according to our current knowledge, biological variables appear to make relatively small contributions to explaining suicide attempts. Starting 20 years ago with a theory of mental pain [2] as the unifying concept of SB would have been wiser. We are not sure how biological factors or severe affective disorders are relevant in completed suicide, but it may be time to acknowledge that it is legitimate to question the assumption of psychiatric textbooks that 80–90% of completed suicides are explained by depression [65]. Psychological autopsies are complex [44–46], but a recent meta-analysis [72] indicated a relatively low prevalence of affective disorders, i.e. 33–51%, around the world, with 34% in North America, where there were high prevalences of substance-related disorders (i.e. 40%) and personality disorders (i.e. 13%). If these figures are correct, it is hard to defend the concept that biological variables are important in US completed suicides when it is not even clear that substance-related disorders or personality disorders are disorders in the medical sense [73].

To change the course of research in the area of suicide after 20 years of mistakes, we propose that suicide researchers should read again and again physician thinkers such as Jaspers [36] and Feinstein [25, 27, 74–76]. Jaspers [36], many years after leaving psychiatry, insisted that psychiatrists ‘must learn to think’ [73]. Feinstein [25, 27, 75] designed ‘clinimetrics’ [74, 76] to deal with complex medical concepts, such as SB. Clinimetric concepts have been applied to psychiatry [76–81]. Feinstein [27] also insisted that EBM [26, 28] has difficulties in dealing with outliers and heterogeneity, but we believe that outliers and heterogeneity are extraordinarily important concepts when looking for ways to understand suicide attempts in Western countries. We have found that biological variables may have small effects in explaining suicide attempts. It is also time to consider that one must be open to the hypothesis that mental illness may not explain the majority of completed suicides in Western countries, as some nonmedical researchers propose [65].

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