31 Antidepressant Medications and Suicide Risk: What Was the Impact of FDA Warning?

Gianluca Serafini, Paola Solano, and Mario Amore

31.1 Introduction

Suicide is one of the most relevant public health issue worldwide as shown by the fact that the World Health Organization (WHO) launched a warning reporting that there will be a 20 % increase of deaths due to suicidal behavior by 2020 [1]. Moreover, the WHO suggested that every 40 s an individual dies by suicide, and many more attempt suicide worldwide. Most cases are related to the presence of a psychiatric condition and in particular more than 50 % of deaths occur in comorbidity with major affective disorders [2]. Overall, 1–2 % of the entire population completed suicide during the life span [3], but suicide risk may be considered generally modest during a specific brief period. Given that numbers of suicide events as well as the size of investigated cohorts of suicidal patients are generally quite small, the main findings of most studies should be interpreted with caution.

As mentioned, some of the most relevant risk factors for suicide include the presence of psychiatric conditions such as major depressive disorder (MDD), in particular if associated with hopelessness or in comorbidity with substance abuse [4–7]. Suicidal behavior and self-harm have been reported to be generally increased in subjects with major depression [8, 9], and antidepressant (AD) medications are commonly used as a conventional treatment option in these patients although they may be also associated with dysphoric-mixed-agitated/psychotic states potentially increasing suicidal risk [10–12].

Recently, the effects of psychoactive treatments on suicidal behavior raise a growing interest among clinicians since contrasting evidence has been reported concerning the effect of these medications on suicide risk. Although AD compounds significantly reduce the severity of depressive symptoms [13, 14], existing evidence also showed that suicide rates and self-harm may increase with the use of these medications especially in younger individuals [15–17].

A large body of literature addresses the need of identifying those AD compounds associated with the higher suicide risk, but robust evidence including reliable randomized controlled trials (RCT) able to inform about the best AD treatment strategy is still lacking to date. Notably, the relationship between AD compounds and suicide events is difficult to investigate, mainly due to the relative low frequency of suicides. According to a recent meta-analysis of data submitted to the US Food and Drug Administration (FDA) including over 350 AD trials and approximately

G. Serafini, MD, PhD (✉) • P. Solano • M. Amore
Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), Section of Psychiatry, University of Genova, IRCCS San Martino, Largo Rosanna Benzi 10, Genova 16100, Italy
e-mail: gianluca.serafini@unige.it

F. López-Muñoz et al. (eds.), *Melatonin, Neuroprotective Agents and Antidepressant Therapy*,
DOI 10.1007/978-81-322-2803-5_31

100,000 patients, only eight suicide deaths had been documented [15].

This chapter aimed to address the relationship between AD compounds and suicidal behavior, first by providing a historical background about the main topic and then by carefully reviewing the most important findings regarding this theme in the current literature. For this purpose, the FDA boxed warning concerning the increased suicide risk related to the use of AD medications will be addressed and discussed both in respect to the whole population and different age groups.

31.2 Historical Background

The initial studies suggesting a possible association between AD treatment and increase of suicidality were essentially case studies dated back to 1991 and reporting that high doses of fluoxetine may be associated with suicidal behavior in adolescents [18]. However, subsequent studies did not universally confirm these results [19]. In May 2003, GlaxoSmithKline advised the FDA in the USA that paroxetine use during the course of a clinical trial has been associated with suicide-related adverse events in pediatric patients [20]. At the end of 2003, the Medicines and Healthcare Products Regulatory Agency, the UK's counterpart to the FDA, sent a letter to all clinicians working in the UK to advice against using fluoxetine in children and adolescents. In October 2004, the FDA reached a split decision (specifically, 15 yes, 8 no) according to which pharmaceutical companies have been dictated to add a "black box warning" (Fig. 31.1) concerning the heightened risk of suicidal thoughts and behaviors in subjects who were using AD medications. In particular, AD medications have been associated with an increased risk of suicidal thinking, feelings, and behavior in young and adolescent subjects. As reported, the warning is about AD medications that may cause de novo "suicidality" in some individuals [21]. The introduction of a "black box" warning represented the most serious warning which was placed in the labeling of a prescription medication. Advertisements that serve to remind health-care professionals of a product's availability (so-called reminder ads) are not allowed for products with "black box" warnings. Moreover, a black box warning does not prohibit the use of a certain compound, e.g., AD drugs in children and adolescents. Rather, it introduces a warning about the risk of suicidality and encourages prescribers to carefully balance this risk associated with AD's use with clinical needs.

However, this FDA warning was rapidly associated with a burning debate since it was argued that it would have discouraged depressed

The results of pediatric depression studies to date raise very important problems. First, the poor effectiveness results, except for Prozac, make it very difficult for practitioners to know what to do to treat a very serious, life-threatening illness.While we believe that these drugs may be effective in children, studies have not shown this to be true. Second, and of equal importance, the analyses we initiated in 2002 appear to show that the drugs in the pediatric controlled depression trials can lead to suicidal behaviors or thinking. While no suicides occurred in the trials, suicides certainly have been reported in treated patients, and the devastating results of these suicides were a critical part of the February 2, 2004, Advisory Committee meeting.

FDA generally supports the recommendations that were recently made to the Agency by the Psychopharmacologic Drugs Pediatric Advisory Committees regarding reports of an increased risk of suicidality associated with the use of certain anti-depressants in pediatric patients. FDA has begun working expeditiously to adopt new labeling to enhance the warnings associated with the use of anti-depressants and to bolster the information provided to patients when these drugs are dispensed.

Fig. 31.1 Extract from FDA black box warning "Antidepressant Drug Use in Pediatric Population," issued 15 October 2004 (http://www.fda.gov/NewsEvents/Testimony/ucm113265.htm)

patients from seeking help and clinicians from prescribing AD medications even if they were clinically indicated [22]. Moreover, a large meta-analysis of placebo-controlled randomized trials including 100,000 patients found that AD medications may increase suicidal behavior till the age of 40 years [23]. Although the exact mechanism involved in the supposed increased suicidality was poorly understood, the assumptions underlying the introduction of the "black box" warning supported the paradoxical idea that AD drugs can have two separate (apparently opposite) effects, one promoting suicidal behavior and the other preventing suicidality, respectively. The hypothesis that does not recognize the preventative effect and assumes only the existence of the promoting effect was not able to explain the protective effect which was observed in older subjects. The relative susceptibility to these two effects seemed to vary according with age. In older subjects the preventative effect tended to predominate, whereas in younger subjects it appeared the opposite. Exactly, the risk may be considered doubled in youths [23] although many suicides and suicide attempts in this population have been missed by the FDA analysis [24].

This controversial topic was further stressed by the study of Gibbon and colleagues [25] who analyzed data on prescription rates for selective serotonin reuptake inhibitors (SSRIs) from 2003 to 2005 in children and adolescents using available data (through 2004 in the USA and 2005 in the Netherlands). SSRI prescriptions in these populations were significantly reduced by approximately 22 % in the USA and the Netherlands after the FDA warnings [25]. According to these data, youth suicide rate increased by 49 % between 2003 and 2005 in the Netherlands with a significant inverse association with SSRI prescriptions, whereas a 14 % increase of youth suicide rates in the USA (2004–2005) has been reported. However, the prescription decline has been observed in 2005 whereas the suicide increase occurred in 2004 [26].

Over the last decade, other researches brought up further claims regarding negative consequences related to the FDA black boxed warning. However, it is difficult to distinguish the effects of the black boxed warning from those of public awareness regarding suicidality. As Stone [26] correctly suggested, although adverse outcomes such as suicides increased in 2005 concomitantly with a dramatic reduction in AD use, the two phenomena may be unrelated. Similarly, although AD administration has been associated with a significant reduction of suicide risk, not necessarily an increase in the prevalence of AD use results in significantly reduced rates of suicide. Therefore, a causal link between the introduction of the black box warning, changes in AD use, diagnosis of depression, and treatment cannot be definitely drawn [27].

Lu and colleagues [28] analyzed a very large cohort of health-care claim data of patients (from 2000 to 2010) including 1.1 million adolescents and 1.4 million young adults and reported a significant reductions in AD use during the course of 2 years after the FDA advisory among adolescents, young adults, and adults. They suggested that, after the FDA warning was issued, the rates of AD use remained below the formerly expected levels according to prewarning patterns in all age groups. This reduction in AD prescriptions was paralleled by a significant post-warning decrease in the rate of new diagnoses of major depression in all age groups (children, young adults, and all adults) by primary care providers. Although the evident reduction of AD prescriptions after the FDA warning, no compensatory use of alternative depression treatments occurred [29]. Unfortunately, the FDA introduction of the black box warning that occurred in 2007 does not seem to be sufficient to attenuate the detrimental effect on depression treatment.

Considering this historical background and the effects related to the introduction of the black box warning regarding suicidality in subjects who were taking AD drugs, the present chapter critically reviews the current literature about the potential associations between AD use and completed/attempted suicide and is mainly aimed to inform clinicians about the relationship between use of modern AD medications and suicidality after the FDA warning.

31.3 The Resonance of the FDA Black Boxed Warning: Antidepressants and Suicide Risk

Different studies investigated the resonance of FDA black boxed warning on suicidality using both experimental and ecological study designs. Here, as follows are summarized studies concerning AD prescribing rates after FDA boxed warning and studies about the increased/reduced suicidality after the black boxed warning, respectively.

31.3.1 Antidepressant Prescribing Rates After FDA Boxed Warning

The issue of AD prescription volumes after the FDA boxed warning has been investigated in different studies, though no concluding evidence about a potential decline in national AD prescribing patterns after the FDA boxed warning was reported according to the majority of studies (Table 31.1). For instance, Mittal and colleagues [30] reported that after a 2-year period, AD prescriptions for depressed children and adolescents in community-based and outpatient clinic settings declined compared to the period before the FDA boxed warning. However, this decline seems to be not persistent during the 5 years following the implementation of the FDA boxed warning. Specifically, the authors reported that during 2002–2003, ADs were prescribed in 4.1 million visits, 3.2 million visits in 2004–2005, and 2.8 million visits in 2006–2007, respectively. Based on these findings, AD prescribing volumes reversed during 2008–2009 with an increase to 3.6 million visits. Importantly, a significant decline in visits related to AD prescribing rates in the post-FDA boxed warning period (2006–2007) has been found compared to 2002–2003. Similarly, Clarke and colleagues [31] retrospectively examined 57,782 youths aged 10–17 and found that both new (incident) and refill AD dispensing continued to decline through 2009 with no sign of leveling off. However, among youths who started AD treatment, the cumulative supply of AD medication remained consistent across the pre- and post-period. This suggested that cumulative treatment episode duration did not decrease, possibly as a function of greater days' supply with each new refill in the post-period. Moreover, the authors reported that prescribers dramatically curtailed preauthorized refills in the post-warning period. Reeves and Ladner [32] suggested that AD-induced suicidality was an uncommon occurrence but even a legitimate phenomenon; therefore, a close monitoring was needed and an adequate follow-up care should be provided for patients after the beginning of an AD treatment. Katz and colleagues [33] investigated the effects of the FDA warning on AD prescribing patterns/outcomes in order to ascertain whether it may be associated with any unintended health consequences. The authors reviewed health-care databases including more than 265,000 Canadian children, adolescents, and young adults to investigate annually changes in the rates of AD prescription and outcomes in these populations in the 9 years before and 2 years after the warning, respectively. This population has been confronted with young adults used as a comparison group since this population was not targeted by the FDA warning. Results demonstrated that the rate of AD prescriptions is reduced among children and adolescents (relative risk (RR) 0.86, 95 % confidence interval [CI] 0.81–0.91) and young adults (RR 0.90, 95 % CI 0.86–0.93). In particular, there has been a reduction of 14 % in the rate of AD prescription among children and adolescents after the warning, whereas rates of newer AD use, except for fluoxetine, declined by 32–40 %. Fluoxetine use increased by 10 % in the period following the warning. Importantly, the rate of completed suicides among children and adolescents raised significantly after the warning (RR 1.25, 95 % CI 1.08–1.44; annual rate per 1000 = 0.04 before and 0.15 after the warning) coupled with no equivalent change in the rate of completed suicides among young adults (RR 1.01, 95 % CI 0.93–1.10; annual rate per 1000 = 0.15 before and 0.22 after the warning). In another study, Wijlaars and colleagues [34] evaluated a cohort of 1,502,753 children and adolescents in

Table 31.1 Evidence about the most relevant studies about AD use and suicide rates before and after the FDA black boxed warning

Study	Type of study	Sample	Main results
Lu et al. [28]	Association between AD use before and after the FDA warning and suicide attempts in patients admitted to hospital or emergency departments	1.1 million adolescents 1.4 million young adults 5 million adults	Safety warnings and widespread media coverage reduced AD use; similarly, suicide attempts among young people increased
Leon et al. [44]	Longitudinal 27-year observational study using prospective assessments of AD-associated suicidal behavior	757 subjects older than 17 years	The risk of suicide attempts or completed suicides was reduced by 20 % among participants taking antidepressant medications
Isacsson and Rich [21]	Longitudinal study on association between AD treatment and suicide rates in adolescents in Sweden during the period between 1992 and 2003 (baseline), and 2004–2010 (after the FDA warning)	845 suicides in the 10- to 19-year age group	The increase occurred among individuals not treated with antidepressant drugs
Barber et al. [38]	Survey carried out by the Centers for Disease Control and Prevention's youth risk behavior	100/100,000 suicides subjects aged 10–17	A reduction from 2000 to 2009 as well as a more recent increase in high school students' self-reported suicidal thoughts, plans, and attempts have been observed
Mosholder and Willy [48]	Meta-analysis based on data from 22 randomized, short-term, placebo-controlled, pediatric trials	2298 pediatric subjects who had been treated with nine different AD medications that were compared to 1952 individuals who received placebo	78 (54 with active drug and 24 with placebo) suicidal adverse events occurred in these trials, but no completed suicides have been reported. Active drug treatment was associated with an almost double rate of serious suicidal events compared with placebo
Hammad et al. [49]	Meta-analysis based on data from 20 trials	4582 pediatric depressed subjects	AD use in pediatric patients is associated with a modestly increased risk of suicidality
Bridge et al. [50]	27 studies published and unpublished randomized, placebo-controlled, parallel-group trials about second-generation antidepressants in subjects younger than 19 years	3241 subjects aged 6–18 with MDD 718 subjects aged 6–18 with OCD 1162 subjects aged 5–18 with other anxiety disorders	There was an increased risk difference of suicidal ideation/suicide attempt across all trials and indications for drug *vs.* placebo (0.7 %; 95 % CI, 0.1–1.3 %), benefits of AD greater compared to the risks
Katz et al. [33]	Reviewed national databases for AD prescription volumes and suicide rates for 9 years before and 2 years after the FDA warning	265,000 Canadian children, adolescents, and young adults	Overall, a 4 % decrease in AD prescription has been observed; suicides among children and adolescents raised after the FDA warning (RR 1.25, 95 % CI 1.08–1.44; annual rate per 1000 = 0.04 before and 0.15 after the warning). No change in suicides among young adults was reported (RR 1.01, 95 % CI 0.93–1.10; annual rate per 1000 = 0.15 before and 0.22 after the warning)

(continued)

Table 31.1 (continued)

Study	Type of study	Sample	Main results
Bailly [43]	Meta-analysis of RCT in pediatric population	1665 subjects aged 5–18	A modest suicidal behavior increase has been reported with SSRI compared to placebo, though no increase was found in completed suicides in pediatric population. Fluoxetine being the most safe
Wohlfarth et al. [51]	A meta-analysis of 22 RCTs on children and adolescents including studies on MDD, OCD, GAD, social anxiety, SSRIs, and SNRIs	3832 children and adolescents	No risk difference in terms of suicide events in anxiety disorders and OCD patients has been found. Conversely, a 1.4 % risk difference for those in the MDD studies (NNH 71.4) has been observed
Kaizar et al. [53]	Meta-analysis of 24 RCTs on children and adolescents with MDD, OCD, anxiety, and ADHD who were treated with citalopram, fluvoxamine, paroxetine, fluoxetine, sertraline, venlafaxine, mirtazapine, nefazodone, and bupropion	1592 subjects aged 6–17 with MDD 319 subjects aged 6–17 with OCD 75 subjects aged 5–17 with ADHD 322 subjects aged 5–17 with anxiety	An increased risk of suicidal thoughts and behaviors has been reported for those with MDD (OR 2.3), but even if the AD was an SSRI (OR 2.2)
March et al. [52]	Meta-analysis of four RCTs on sertraline in MDD and OCD	987 subjects aged 10–17 with MDD; 286 aged 7–15 with OCD	According to two MDD studies, the risk difference in terms of suicidal thoughts and behaviors was increased for sertraline to 1.56 % (NNH 64.2). No difference was reported in OCD studies with sertraline
Hammad and Mosholder [54]	Survey carried out by the Centers for Disease Control and Prevention's youth risk behavior	9/100,000 suicides in the USA in adolescents aged 15–19 2/100,000 suicides in the USA in adolescents aged 10–14	The FDA warning may have discouraged the appropriate use of ADs in the treatment of child and adolescent depression
Tiihonen et al. [63]	Ecological cohort study on Finnish adolescents with a follow-up of 3.4 years	15,390 Finnish patients aged 10–19 hospitalized for a suicide attempt	RR for suicide attempts was 1.84. Overall, 44 suicide deaths were reported with no differences in those who were taking antidepressants or not, except for paroxetine (RR 5.44)
Leon et al. [61]	A naturalistic study on three decades of prospective assessment propensity quintile-stratified safety analyses	All ages Unexposed to AD 3433 Exposed to AD 3283	The risk of suicide attempts or completed suicides was significantly reduced when participants received antidepressants
Gibbons et al. [57]	Cross-sectional study aimed to evaluate the association between AD prescription rate and suicide rate in children prior to the FDA findings	933 suicides of children aged 5–14	Higher SSRI prescription rates were associated with lower suicide rates in children and adolescents

Olfson et al. [35]	Cross-sectional study aimed to assess suicide rates for subjects aged 10–19 together with national AD prescriptions	10,604 adolescents receiving AD treatments	Overall, a 1 % increase in the use of ADs in adolescents was associated with a reduction in suicides by 0.23/100,000 adolescents per year
Hall and Lucke [58]	Australian prescription data in general practice for subjects aged 15 or older matched to suicide rates for the same age group	3250 subjects aged 15 or older	Suicide rates were inversely related to AD prescriptions in this age group
Sondergard et al. [59]	Register linkage study on subjects aged 10–17 aimed to evaluate AD prescriptions and suicide	2569 adolescents	SSRI treatment and suicidal behavior were not linked. It has been estimated that none of the suicides ($n=42$) had been treated with an SSRI 2 weeks prior to their suicide
Kamat et al. [62]	Meta-analysis on children and adolescents' AD prescriptions and suicide rates	12,865 children and adolescents	A significant positive correlation between suicide rates and AD rates ($p=0.031$) was reported
Simon and Savarino [60]	A naturalistic study on children and adolescents linking new episodes of depression, AD prescription, and treatment type with suicide attempts	131,788 children and adolescents	The highest risk of suicide attempt was observed in the month before the beginning of AD treatment, but the risk declined in the months after starting the treatment

AD Antidepressant, *FDA* Food and Drug Administration, *GAD* Generalized Anxiety Disorder, *MDD* Major Depressive Disorder, *NNH* Number Needed to Harm, *OCD* Obsessive Compulsive Disorder, *RR* Relative Risk, *SNRIs* Serotonin and Norepinephrine Reuptake Inhibitors, *SSRIs* Selective Serotonin Reuptake Inhibitors

The Health Improvement Network, a UK primary care database. Trends in the incidence of depression, symptoms, and AD prescribing were examined during the period 1995–2009, accounting for deprivation, age, and gender. The authors used segmented regression analyses to evaluate changes in prescription rates. Overall, 45,723 (3 %) children had at least one depression-related entry in their clinical records. Specifically, 16,925 (1 %) children have been treated with SSRIs. A decrease of SSRI prescription rates from 3.2 (95 %, CI: 3.0, 3.3) per 1000 person-years at risk (PYAR) in 2002 to 1.7 (95 %, CI: 1.7, 1.8) per 1000 PYAR in 2005 and a subsequent increase to 2.7 (95 %, CI: 2.6, 2.8) per 1000 PYAR in 2009 have been reported. Prescription rates of some contraindicated SSRIs such as citalopram, sertraline, and especially paroxetine dropped dramatically after 2002, whereas AD rates of fluoxetine and amitriptyline remained quite stable. However, rates for all ADs, except paroxetine and imipramine, increased again after 2005. These results recommend caution for general practitioners (GPs) in detecting depression and prescribing ADs following the FDA warning. Consistently with Olfson and colleagues' [35] evidence, a plausible explanation is that the FDA warnings slowed previous growth in the rate of AD treatment.

31.3.2 Increased Suicidality After the Black Boxed Warning

Lu and colleagues [28] conducted a large study including approximately 1.1 million of adolescents, 1.4 million of young adults, and 5 million adults. Specifically, the authors investigated associations between AD use before and after the warning and suicide attempts in patients admitted to hospital or emergency departments. They found that safety warnings concerning ADs and widespread media coverage reduced AD use, but simultaneously suicide attempts among young subjects increased. This study has been criticized by several authors [24, 27, 36–39] who questioned the sensitivity of the proxy measure (e.g., the proportion of suicide attempts by psychotropic drug poisoning including both intentional and unintentional overdoses) that later has been considered by the same authors as an imperfect proxy for suicide attempts [40]. In addition, the authors subsequently suggested that more direct analyses of suicide attempts and deaths seem to indicate no clear increase of suicide attempts after the FDA warnings [40]. In fact, only a small decrease of adolescent suicides and no change in the fraction of young adults who receive ADs were found. Furthermore, based on the Centers for Disease Control and Prevention data, most self-harm injuries in youths do not involve poisoning, and just half of emergency visits for psychotropic poisonings are intentional in nature [28, 41]. Another criticism that has been raised concerns the fact that not all intentional self-harm in youths reflects suicidal intent in clinical practice [42]. Bailly [43] reported mixed evidence and suggested that relative to placebo, SSRIs are efficacious for pediatric affective disorders although they may be associated with a modest increase in the occurrence of both suicidal ideation and behavior. However, the study showed that SSRI utilization was overall associated with a significant decrease in the suicide rates in children and adolescents, presumably due to their efficacy, relevant treatment adherence, and low toxicity in overdose.

Leon and colleagues [44] reported in a longitudinal, observational study with prospective assessments for up to 27 years which was conducted in five US academic medical centers that AD medications were associated with a significant reduction in the risk of suicidal behavior. Quintile-stratified, propensity-adjusted safety analyses using mixed-effect grouped-time survival models show that the risk of suicide attempts or suicides was reduced by 20 % among participants taking ADs (hazard ratio, 0.80; 95 % CI, 0.68–0.95; $z = -2.54$; $p = 0.011$).

Other authors [45] hypothesized that the warning, contrary to its intention, may have increased young suicides by leaving a number of suicidal young individuals without treatment with ADs. In particular, they analyzed individual data of all 845 suicides in the 10- to 19-year age group in

Sweden at the time frame 1992–2003 (baseline) and 2004–2010 (after the warning). Importantly, after the warning suicide in this age group increased for five consecutive years (60.5 %). The increase occurred among individuals which were not treated with ADs. Finally, there is also evidence suggesting that the decision to introduce the "black box" warnings was based on biased data and invalid assumptions [21].

Isacsson and Rich [21] suggested that the FDA decision was unsupported by the observational data regarding suicide in young people existing in 2003. The authors recommended that drug authorities may reevaluate the imposed warnings on AD drugs by analyzing the current public health consequences after the introduction of the warnings. They also reported that clinicians should be encouraged to treat depression in young individuals using ADs if indicated. According to the authors' suggestions, clinicians have to be aware about the increased suicide risk in depressed young subjects, closely monitoring this population of patients.

31.3.3 Decreased Suicidality After the Black Boxed Warning

There are studies that do not show an increase in suicide attempts or deaths in young people after the FDA warnings [38]. For example, based on a survey which was carried out by the Centers for Disease Control and Prevention's youth risk behavior, a reduction from 2000 to 2009 and, conversely, a more recent increase in high school students' self-reported suicidal thoughts, plans, and attempts have been observed [46]. Two national samples of hospital visits reported no increasing trend in young self-harm after the 2003–2004 FDA warnings [46]. Consistently with the aforementioned results, no increase in youth self-harm has been registered by the California's EPIC website [47].

Different studies confirmed these results, for instance, three meta-analyses of clinical trial data demonstrated that AD treatment increases, rather than decreases, the risk of suicidal behaviors in youths and adolescents [48–50].

In particular, Mosholder and colleagues [48] conducted a meta-analysis based on data from 22 randomized, short-term, placebo-controlled, pediatric trials involving 2298 pediatric subjects who had been treated with nine different AD medications that were compared with 1952 individuals who received placebo. The authors reported that overall, 78 (specifically, 54 with active drug and 24 with placebo) suicidal adverse events occurred in these trials, but no completed suicides have been reported (combined incidence rate ratio across all trials for serious suicidal adverse events = 1.89). Therefore, active drug treatment was associated with an almost double rate of serious suicidal events compared with placebo [48]. The second meta-analysis, Hammad et al. [49] included only 20 trials in the risk ratio analysis of suicidality among all placebo-controlled trials submitted to the FDA. No completed suicides have been reported in any of these trials, and the multicenter trial was the only study in which a significant risk ratio (4.62; 95 % confidence interval [CI], 1.02–20.92) was observed. As reported, 1.66 (95 % CI, 1.02–2.68) was the overall risk ratio for SSRIs in depression and 1.95 (95 % CI, 1.28–2.98) for all medications across all indications. In conclusion, the authors suggested that AD drug use in pediatric patients is associated with a modestly increased risk of suicidality.

Interestingly, Wohlfarth and colleagues [51] conducted a meta-analysis on 22 RCTs in child and adolescent populations ($n = 3832$) including samples of patients with MDD, obsessive compulsive disorder (OCD), generalized anxiety disorder (GAD), and social anxiety who were treated with SSRIs and SNRIs. The authors concluded that there was no risk difference in terms of suicide events in the sample of patients who were treated for anxiety disorders and OCD, whereas there was a risk difference for those in the MDD studies of 1.4 % (number needed to harm (NNH) 71.4). Similar results have been reported by March and colleagues [52] who analyzed four RCTs conducted using sertraline in MDD and OCD and found that in the two MDD studies, the risk difference for both suicidal thoughts and behaviors was increased of 1.56 %

for sertraline (NNH 64.2). Moreover, suicidal thoughts and behaviors associated with sertraline were more frequently observed in depressed children than depressed adolescents. However, there was no increase in suicidal thoughts and behaviors associated with sertraline when used for the treatment of OCD. These results suggested that the increase of suicidality in children and adolescents who were treated with SSRI compounds could be presumably a factor related to psychopathology rather than a specific drug-related effect. Notwithstanding with these results, Kaizar and colleagues [53] conducted a meta-analysis of 24 RCTs with a sample of children and adolescents with MDD, OCD, anxiety, and attention deficit hyperactivity disorder (ADHD). Moreover, citalopram, fluvoxamine, paroxetine, fluoxetine, sertraline, venlafaxine, mirtazapine, nefazodone, and bupropion demonstrated an increased risk of suicidal thoughts and behaviors for those with MDD (OR 2.3), in particular whether the AD was an SSRI (OR 2.2).

Furthermore, Bridge et al. [50] included 27 studies published and unpublished randomized, placebo-controlled, parallel-group trials about second-generation AD medications in subjects younger than 19 years. Based on pooled risk differences in rates of primary study-defined measures of responder status, this study demonstrated that while there was an increased risk difference of suicidal ideation/suicide attempt across all trials and indications for drug vs. placebo (0.7 %, 95 % CI, 0.1–1.3 %) (number needed to harm, 143 [95 % CI, 77–1000]), the pooled risk differences within each indication were not statistically significant. In this study, however, similarly to the previously mentioned reports, there were no completed suicides. According to the main results, the authors reported that benefits of AD medications seem to be greater compared to the risks from suicidal ideation/suicide attempt across indications. Findings from these meta-analyses are generally in line with data on self-harm derived by WISQARS nonfatal emergency department visits which were conducted on subjects aged 10–17 that showed increased rates of self-harm in years 2004 and 2005, concomitantly with the timing of the FDA warnings.

Overall, no concluding evidence seems to emerge, and the use of AD in young and adolescent populations still remains a tricky matter of concern according to the current knowledge about this topic.

31.4 Antidepressant Drugs and Suicide Risk: The Contribution of Ecological and Postmortem Studies

Ecological studies, despite a geographic variability related to AD use, demonstrated an inverse association between suicide rates and AD prescription volumes. Unfortunately, ecological population-based approaches are usually limited, and cautions are necessary when interpreting data.

Hammad and Mosholder [54] warned against the danger of a discouraging effect that could lead to a decrease in the appropriate use of AD in the treatment of child and adolescent depression. Also other authors highlighted the risk on the potential for discouraging appropriate use of AD drugs based on the sparked debate upon the FDA warning [15, 49, 55]. This could be mainly associated to the unintended consequence of eventually exposing more patients than occurring with AD drugs to the suicide risk of untreated depression [25]. These concerns were enhanced by the upturn in the 2004 US rate of adolescent suicide [25]. Moreover, significant falls were also reported in AD drug prescriptions for pediatric patients after the regulatory agency actions [25, 29, 55]. However, 6 years later data from the Centers for Disease Control and Prevention on the overall trend in suicide rates among adolescents showed that the rate of suicide decreased after the unexplained increase of 2004 [56] whereas in 2007, the most recent year with available data, the rates were the lowest reported in the last 25 years.

Some studies have been also carried out prior to the FDA warning. Gibbons and colleagues [57] examined the association between AD prescription rate and suicide rate in children aged 5–14 years by analyzing associations at the

county level across the USA. After adjustment for sex, race, income, access to mental health care, and county-to-county variability in suicide rates, higher SSRI prescription rates have been associated with lower suicide rates in children and adolescents. The aggregate nature of these observational data precludes a causal interpretation of the main findings, but the authors suggested that more SSRI prescriptions are associated with lower suicide rates in children and may reflect AD efficacy, treatment compliance, and better-quality mental health care. Furthermore, Olfson and colleagues [35] examined regional suicide rates for subjects aged 10–19 years with national AD prescriptions (1999–2000) and reported an inverse relationship between AD and suicide in this age group. Specifically, a 1 % increase in the use of AD in adolescents was associated with a reduction of suicides by 0.23/100,000 adolescents per year. Hall and Lucke [58] confronted Australian prescription data in general practice for subjects aged 15 or older which were matched to suicide rates for the same age group (1991–2001) suggesting that suicide rates were inversely related to AD prescriptions. The Danish pharmacoepidemiological register linkage study ($n=2569$) concerning prescriptions and suicide, 1995–1999, demonstrated no link between SSRI treatment and suicide in subjects aged 10–17 years. As suggested by Søndergård and colleagues [59], none of the 42 suicides had been treated with an SSRI 2 weeks prior to their suicide. In addition, Simon and Savarino [60] conducted a naturalistic study in a sample of children and adolescents linking new episodes of depression, AD prescription, and treatment type with suicide attempts ($n=131,788$), 1996–2005. Subjects have been followed 90 days prior to starting treatment and 180 days following the commencement of treatment. The risk of suicide attempts was highest in the month before the initiation of an AD treatment and dropped in the months after starting treatment regardless of whether they are receiving ADs from primary care physician or psychiatrist or psychotherapy.

Notwithstanding with the FDA's black boxed warning, an observational study on mood disorders that considered three decades of prospective assessment propensity quintile-stratified safety analyses found that the risk of suicide attempts or suicides was significantly reduced when participants received AD medications [61]. However, Kamat et al. [62] reported data from the Organisation for Economic Co-operation and Development (OECD) health dataset (1995–2008) showing a significant positive correlation between suicide rates, AD rates ($p=0.031$), and unemployment ($p=0.028$). These results also showed a significant negative correlation between suicide rates and inpatient psychiatric beds ($p=0.039$). However, the actual coefficients are less than ±0.16 indicating weak relationships and, after adjusting for other variables, the only variable that resulted statistically significantly associated with suicide rates is AD prescribing ($p=0.005$, $r^2=0.09$).

Tiihonen and colleagues [63] conducted an ecological cohort study including 15,390 Finnish patients aged 10–19 years which were hospitalized for a suicide attempt with a follow-up of 3.4 years (from 1997 to 2003) in order to investigate the relationship between AD treatment and suicides. The authors reported that the adjusted RR for suicide attempts in those using ADs was significant (1.84). Moreover, they reported 44 deaths in those aged 10–19 years with no differences in those who were treated or not treated with AD drugs, except for paroxetine for which an RR of 5.44 was reported.

However, ecological data could not establish cause-effect associations nor determine whether the changes in prescribing were due to untreated depression with drugs or prescription of fewer AD drugs for other conditions. Although being careful for the unintended consequences of regulatory agency actions is important, ecological data may be not the best guide to ascertain whether drugs are being used appropriately in a specific population of patients. Recently, Gusmao and colleagues [64] conducted a large naturalistic study that aimed to describe trends in the use of AD and rates of suicide in Europe, adjusted for gross domestic product, alcohol consumption, unemployment, and divorce. Moreover, the study explored whether any observed reduction in the

rate of suicide in different European countries preceded the trend for increased use of AD medications. Data were obtained for 29 European countries between 1980 and 2009 and showed an inverse correlation in all countries between recorded standardized death rate (SDR) for suicide and AD defined daily dosage (DDD), with the exception of Portugal. Every unit increase in DDD of an AD per 1000 people per day, adjusted for these confounding factors, reduces the SDR by 0.088. The correlation between DDD and suicide-related SDR was negative in both time periods considered, albeit more pronounced between 1980 and 1994. Thus, the authors concluded that suicide rates have tended to decrease more in European countries where there has been a greater increase in the use of AD drugs. Gusmao and colleagues' [64] findings underline the importance of the appropriate use of AD medications as part of routine care for people diagnosed with depression, therefore reducing the risk of suicide.

There are also postmortem studies about AD drugs and suicidality. In a large meta-analysis concerning AD treatments and children and adolescent suicidality, Gordon and Melvin [19] examined 11 meta-analyses of placebo-controlled trials, 17 pharmacoepidemiological studies, one meta-analysis of observational studies, and six postmortem studies. Based on the six postmortem studies, the authors suggested that if AD drugs are related to adolescent suicide events, AD medications should be presumably present in toxicology assays of adolescent suicide victims. Therefore, they assessed six toxicology studies for the presence of AD drugs in adolescents who died by suicide. Their findings suggested that it was reasonably uncommon for adolescents who have died by suicide to have been taking newer AD drugs, such as SSRI at therapeutic doses. The infrequent presence or absence of AD medications at autopsy suggests either the adolescent was not prescribed the AD or was not taking it in the days prior to their suicide [45, 65–68].

Several limitations should be considered when analyzing the main results of postmortem studies. First, not all toxicology assays were available for those who died by suicide. Unfortunately, these studies were not able to exclude subjects who had an injury to death period of less than 3 days [68]. Finally, it was not possible to know how many subjects may have withdrawn their AD treatment (AD withdrawal has been reported as a mechanism increasing suicidal behaviors) [45].

31.5 Antidepressant Use and Suicide Risk in Different Age Groups

Investigating the effect of specific medications in specific populations of patients is of paramount importance due to the differences of life span suicidal behaviors, psychopathology, and brain functioning [69].

31.5.1 Adults and Elderly

Recently, Gibbons and colleagues [70] concluded that AD drugs lowered suicidality relative to placebo among adult patients while demonstrating no difference in suicidality among youths. They suggested that AD medications possessed a robust efficacy in reducing suicidal behavior when compared with placebo. Further evidence has been provided by Erlangsen and Conwell [71], who identified an age-dependent decline in suicide rate for AD recipients. One possible explanation could be that older adults respond better to AD drugs than younger age groups. In addition, based on the increasing gap with age between estimated prevalence of depression and AD prescription rate in individuals dying by suicide, there is the urgent need to assess major depression in the elderly. Logistic regression analyses showed a 2–3 % decline in suicide rates with each additional year of age for men and women in treatment with AD compounds, respectively. Conversely, an opposite trend was found for untreated subjects. Moreover, fewer persons aged 80+ dying by suicide had received AD prescriptions during the last months of their life when compared with younger subjects [71]. Aiming to evaluate the AD use volume in different age group in respect to suicide risk, Phillips

and Nugent [72] reported an overall increase in AD use in all age groups coupled with a decrease in suicide rates for the young individuals and elderly. The elderly showed the largest increase in AD usage coupled with the biggest decrease in suicide rates, whereas only a moderate increase of suicide rates for the middle-aged group was found. Moreover, immediately after the FDA issued the black box warning, the Committee on Safety on Medicines (CSM) in the United Kingdom (UK) reported that in adult depression SSRIs remain beneficial. In addition, Gunnell and colleagues [73] carried out a meta-analysis of data from the Medicines and Healthcare Products Regulatory Agency of published and unpublished RCTs of SSRIs which were compared with placebo in adults and elderly. Although they found no evidence that SSRIs increased the risk of suicide or suicidal thoughts when compared with placebo, they reported weak evidence for an increased risk of self-harm (OR¼1.57, 95 % CI 0.99–2.55). In the same year, Fergusson and colleagues [74] found, in another meta-analysis including published RCTs of SSRIs which were used in any disorder, an increase in suicide attempts for adult patients receiving SSRIs when compared with placebo (OR = 2.28, 95 % CI 1.14–4.55) or therapeutic interventions other than tricyclic AD drugs (OR = 1.94, 95 % CI 1.06–3.57).

There are also studies reporting an inverse correlation between elderly suicide rates and AD prescription rates. For example, Shah and colleagues [75] reported that there was no significant correlation between elderly suicide rates and AD prescription rates in the large British National Formulary categories, individual psychotropic drug groups, and individual psychotropic drugs.

31.5.2 Children and Adolescents

The FDA black boxed warning concerning the possible association between children and adolescent suicide rate and AD treatments stimulated debates, and several studies about this topic appeared in literature (*see above*), though no concluding evidence has been reported [76].

A large meta-analysis of 35 randomized controlled trials of AD treatments compared with placebo in pediatric and adolescent patients with a total sample of 6039 individuals has been recently conducted. Suicidal behavior, suicidal ideation, and suicidal behavior or ideation were examined as suicide-related outcomes. There were trends indicating that active treatments increased the risk of these events in absolute terms. Regarding efficacy, the results showed that AD treatments did have a statistically significant effects compared to placebo, but the effect was less for the trials which were conducted on major depression. Overall, there was evidence of an increased risk in suicide-related outcomes on AD treatments, while AD treatments were also shown to be efficacious [77]. Phillips and Nugent [72] reported a decrease in overall suicide rates for the young and elderly coupled with an increase in AD use in all age groups. Hetrick and colleagues [78] meta-analyzed 16 RCTs including SSRIs on 2240 children and showed an increased risk of suicidal ideation and behavior in individuals receiving an SSRI compared with those receiving a placebo (RR 1.80; 95 % CI 1.19, 2.72). The Treatment for Adolescents with Depression Study (TADS) [52] is a large RCT on adolescents with major depression that included treatment with fluoxetine alone, cognitive behavioral therapy alone, combined treatment, and placebo. Since this study was the first to prospectively define suicide-related events in youths, thus its findings on suicidality are also historically important to consider when addressing the risk and benefits of ADs in youths. In particular, this study demonstrated that subjects receiving fluoxetine had lower suicidal ideation at follow-up than after the beginning of treatment as well as when compared with those in the placebo group.

Henry and colleagues [79] carefully reviewed a series of published and unpublished efficacy and safety data regarding AD use in children and adolescents. Based on epidemiological data, the authors failed to confirm the relationship between newer AD prescription and completed suicide in large populations of youths. In addition, Hetrick et al. [80] conducted a large Cochrane review on newer-generation AD compared to placebo in

children and adolescent depression considering 19 trials including 3335 participants. They found that there was evidence of an increased risk (58 %) of suicide-related outcome for those on AD medications compared with placebo (17 trials; $N = 3229$; RR 1.58; 95 % CI 1.02–2.45). This equated to an increased risk in a group with a median baseline risk from 25 in 1000 to 40 in 1000. The authors suggested caution is needed in interpreting the main results of this meta-analytic study considering the methodological shortcomings related to the internal and external validity. They also stated that both the size and clinical significance of the present findings need to be replicated. In summary, fluoxetine could be the medication of first choice based on the guideline recommendations, but, importantly, clinicians have carefully considered that an increased risk of suicide-related outcomes has been reported in those treated with AD drugs.

31.6 Association Between Type of Antidepressant Medications and Suicide Risk

Some reports suggested an increase of both suicide ideations and behaviors in patients of all age groups treated with specific AD medications.

31.6.1 Adults and Elderly

A study in a large cohort of patients aged 20–64 and diagnosed with major depression showed significant associations between different types of administered AD drugs and rates of completed and attempted suicides or self-harm. The group of AD medications classified as "other AD medications" (mainly including venlafaxine and mirtazapine) has been associated with the highest rates of both completed and attempted suicides or self-harm. Conversely, the use of mirtazapine, venlafaxine, and trazodone was associated with an increased risk of attempted suicides or self-harm compared with the most commonly prescribed AD, citalopram [81]. Multiple evidences have suggested that both venlafaxine and mirtazapine are associated with a greater risk of suicide and self-harm at a population level [82, 83]. Clinicians should be careful when prescribing these drugs in patients at high risk for suicide given the existence of published studies supporting the assumptions that they are the most lethal non-TCA AD drugs when taken in overdose [84]. Nevertheless, clinical trials—subject to their own sources of bias—indicated that venlafaxine and mirtazapine are at least as effective as SSRIs in alleviating depressive symptoms [85, 86].

Furthermore, Coupland and colleagues [82] reported that SSRIs were associated with the highest adjusted hazard ratios (HRs) for attempted suicide/self-harm (5.16, 95 % CI 3.90–6.83). There was no evidence that SSRIs or drugs in the group of other AD medications were associated with a reduced risk of any of the adverse outcomes compared with TCAs; however, they may be associated with an increased risk of specific outcomes. Moreover, Garlow and colleagues [87] found that compared to placebo, fluoxetine was not associated with a clinically significant increase in suicide ideation among adults with minor depressive disorder throughout a 12-week treatment study.

Conversely, Grunebaum and colleagues [88] carried out a post hoc analysis of data from a randomized, double-blind, 8-week clinical trial of the SSRI paroxetine controlled release ($n = 36$) vs. the norepinephrine-dopamine reuptake inhibitor bupropion extended release ($n = 38$) in patients aged 18–75 with DSM-IV major depressive disorder and past suicide attempts or current suicidal thoughts. The authors suggested a pathway by which SSRI treatment may exert a stronger effect compared with norepinephrine-dopamine reuptake inhibitor treatment on the possible reduction of suicidal thoughts during the initial weeks of pharmacotherapy in these patients with higher suicide risk. There was a strong effect on HDRS psychic depression (depressed mood, guilt, retardation, helpless, hopeless, worthless) (estimate = −2.2; 95 % CI, −3.2 to −1.1; t67.16 = −4.01; $P < 0.001$), that is one of the clusters most strongly correlated to suicidal ideation. The net drug effect demonstrated that mean psychic depression score was 2.2 points lower after 1 week of paroxetine

treatment relative to bupropion treatment. The significance level of this effect was <0.001 at weeks 1 and 2, 0.012 at week 3, and 0.051 at week 4, respectively, whereas results for other depression scale factors were not significant ($p > 0.05$). Makris and colleagues [89] used Swedish Registers and identified 12,448 suicides with forensic data for AD medications and information on inpatient-treated mental disorder during the period 1992–2003. Higher suicide seasonality was found for individuals treated with SSRIs compared to those with other AD treatments or without any AD treatment. The finding is more evident for men, violent suicide methods, and those without history of inpatient treatment.

Furthermore, Valenstein et al. [90] analyzed a sample of veterans with major depression for new AD starts (1999–2004) and found that most AD drugs did not differ in terms of suicide death. However, across several analytic approaches, though not instrumental variable analyses, fluoxetine and sertraline have been associated with a lower risk of suicide death than paroxetine. These findings are in line with the FDA meta-analysis including randomized controlled trials and reporting a lower risk for "suicidality" for sertraline together with a trend toward lower risks with fluoxetine compared with other AD medications.

Zisook and colleagues [91] analyzed 665 patients in the single-blind, 7-month randomized trial Combining Medications to Enhance Depression Outcomes study. Specifically, participants received escitalopram plus placebo, bupropion sustained release (SR) plus escitalopram, or venlafaxine extended release (XR) plus mirtazapine. Baseline ideation did not affect depressive symptom outcome. Bupropion-SR plus escitalopram most effectively reduced suicidal ideation. According to the main findings, venlafaxine-XR plus mirtazapine may pose a higher risk of suicide attempts.

A further caveat concerning the increased suicide risk during a second treatment with a different AD medication needs to be mentioned. Examining data collected between July 2001 and September 2006 from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D), Perlis and colleagues [92] found that of 1240 subjects entering level 2 with a score less than 3 in the suicide item, 102 (8.2 %) experienced emergence or worsening of suicidal thoughts/behaviors. Emergence or worsening at level 1 was strongly associated with reemergence or worsening at level 2 (crude OR = 4.00 [95 % CI, 2.45–6.51], adjusted OR = 2.95 [95 % CI, 1.76–4.96]). Relevantly, overall magnitude of risk was similar among next-step pharmacological augmentation vs. switching.

These results suggest that individuals who experience emergence or worsening of suicidal thoughts or behaviors with one AD treatment may warrant closer follow-up during the next-step treatment, as these symptoms may recur regardless of which modality is selected.

31.6.2 Children and Adolescents

There are studies suggesting an increase of suicide ideations/behaviors in children and adolescent patients treated with specific AD medications. Cooper and colleagues [93] conducted a retrospective cohort study including 36,842 children aged 6–18 years recruited between 1995 and 2006 who resulted new users of at least one of the specified AD medications. The authors reported that there was no evidence that risk of suicide attempts significantly differed for commonly prescribed SSRI/SNRI AD drugs. This study is bolstered by the presence of 419 cohort subjects who had a medically treated suicide attempt and four completed suicides in the whole sample. Furthermore, the adjusted rate of suicide attempts did not significantly differ among current users of SSRI and SNRI AD drugs compared with users of fluoxetine. Notably, users of multiple AD medications concomitantly had increased risk for suicide attempt. Moreover, based on the original venlafaxine publication, only 6 % of patients receiving venlafaxine experienced suicide-related events compared with 0.6 % receiving placebo [94]. After these data were carefully recorded by a second group of researchers, the numbers changed to 4.4 % of patients receiving venlafaxine compared with 0 % receiving placebo, respectively [50]. Either

way, venlafaxine has been associated with increased suicidality in adolescents, although this finding did not get adequate attention by a clinical point of view. Schneeweiss and colleagues [83] conducted a large 9-year observational study in Canada on 20,906 adolescents aged 10–18, who initiated a script for an AD with recorded depression matched with hospitalization for self-harm and suicide. Of those adolescents with a new diagnosis of depression, 266 attempted suicide, and three died of suicide in the first year of use. In addition, there were no differential effects of any of the individual SSRIs and TCAs. Whittington and colleagues [95] in a meta-analysis including five RCTs on suicide-related events and AD prescriptions in children and adolescents found that relative to fluoxetine, paroxetine, and sertraline, venlafaxine was most likely to be associated with suicide-related events. Finally, fluoxetine was likely to be associated with suicidal behavior or attempted suicide. The results were qualified due to the wide confidence intervals.

Furthermore, Miller and colleagues [96] conducted a study comparing two age groups for suicidality and new AD treatment. They used a population-based health-care utilization data with a total of 102,647 subjects aged between 10 and 24 years and 338,021 individuals aged between 25 and 64 years. Among the 10–24-year-old group, prior to propensity score matching, 75,675 initiated SSRI therapy and 5344 a treatment with SNRIs. There were 5344 SNRI users and 10,688 SSRI users after matching. Among the older cohort, 36,037 SNRI users were matched to 72,028 SSRI users (from an unmatched cohort of 225,952 SSRI initiators). Regardless of age group, patients initiating SSRIs and those initiating an SNRI had similar rates of deliberate self-harm. These results were not changed even after restricting to patients with no AD use in the past 3 years. However, Hetrick et al. [80] in their large Cochrane review focused on newer generation of AD compared to placebo in children and adolescent depression and reported no evidence that the magnitude of intervention effects compared with placebo was modified by individual drug class.

Finally, Hysinger and colleagues [97] reported that suicidal behavior among early and late adolescents who were taking AD medications differed in terms of methods used, previous psychiatric history, and proximal symptoms. Of the 250 cases which were reviewed, 65.6 % were female, 26.4 % were aged 10–14 years, and approximately one-half of the sample had a positive history of suicide attempts. It has been found that medication ingestion was the most frequent method of suicidal behavior for both early and late adolescents. However, early adolescents were significantly more likely to use hanging as a suicide method, to have a history of sexual abuse, and significantly less likely to have a history of substance abuse when compared to late adolescents. In addition, early adolescents were also more likely to have a history of a psychotic disorder and report hallucinations before the suicide attempt when compared to late adolescents.

31.6.3 All Age Groups

There are also studies addressing the association between AD use and method of suicide. Phillips and Nugent [72] reported a decrease in overall suicide rates for the young and elderly but underline an increase of suicide rates for the middle aged despite an increase in AD use in all age groups. Firearm suicides in men and women declined, but suicide by drug poisoning rose, particularly in women. In young males and elderly both males and females, better treatment of severe depression may have contributed to declining suicide rates. However, rising rates of prescription drug use are associated with higher levels of suicide by drug poisoning.

31.7 Studies that Did Not Find a Significant Association Between Antidepressant Use and Suicide Risk

There are studies in the current literature that fail to report any association between AD use and suicide rates. For instance, using a

population-based cohort study within the Dutch Integrated Primary Care Information (IPCI) database, Cheung and colleagues [98] did not show any association between the different AD drug classes and suicide attempts overall nor during the first weeks of treatment. Furthermore, no increased risk in the initial treatment period nor after restricting analyses to specific indication or age and gender groups was reported. Although the number of reported cases of suicide attempts was low as reported by the same authors, the study did not demonstrate an increase in terms of suicide risk after starting treatment with any type of AD medication.

In addition, Coupland and colleagues [82] conducted a cohort study using a large UK primary care database in order to quantify associations between different AD medications and suicide as well as deliberate self-harm (including suicide attempts) during the first 5 years of follow-up for adults diagnosed with major depression. Using citalopram as a reference, the authors found no differences in the suicide risk related to individual SSRIs or between SSRIs and TCAs. However, they also reported that the hazard ratio for suicide increased significantly during treatment with the venlafaxine and mirtazapine relative to SSRIs (2.6, 95% confidence interval 1.7–4.0). Interestingly, similar findings were reported for self-harm. Odds of self-harm increased with trazodone and decreased with amitriptyline. Across all AD drugs, hazard ratios for self-harm and suicidal behavior were increased during the first 28 days of treatment and during the 28 days after treatment discontinuation for completed suicides, respectively. However, when interpreting these results, it's important to pay attention to drug dosages. In Coupland and colleagues' study [82], a defined daily dose (DDD) of one corresponds to the generally accepted minimum effective AD dosages (e.g., 20 mg for citalopram and fluoxetine, 75 mg for amitriptyline). Most of the exposure to SSRIs in this study occurred at doses >0.5 DDD or >10 mg of citalopram as for the "other" AD medications. However, 64% of person-years exposure to TCAs occurred at doses ≤0.5 DDD, corresponding to ≤37.5 mg of amitriptyline. Some of these differences may be explained by the fact that TCAs often require a slower titration than other AD medications. Clinicians may also be conservative in their dosing as reflected, for example, in the National Institute for Health and Care Excellence (NICE) guidelines, which suggest that low dosages of TCAs may be maintained if clinical response is achieved (www.nice.org.uk/guidance/cg90). However, lower TCAs dosages can be used in a variety of other indications such as insomnia or headaches, so hazard ratios for the TCAs in Coupland and colleagues' study may be underestimated based on an indication bias. As emphasized by the same authors, the study results may be vulnerable to indication bias and, although conducted on large cohorts, may lack of sufficient power. Unfortunately, this study fails to show how patients may individually respond to specific AD drugs as well as how starting AD drugs or withdrawing from them may differentially confer suicide risk. It is likely that the association between higher suicidality and changes in AD treatment could be due to the fact that treatment changes often occur in periods of higher suicide risk.

Dubicka and colleagues [99] conducted a large meta-analysis to determine the pooled risk of self-harm and suicidal behavior in youths from randomized trials of newer ADs in order to calculate odds ratios for the combined data. The authors found that self-harm or suicide-related events occurred in 71 of 1487 (4.8%) depressed youths who were treated with ADs vs. 38 of 1254 (3.0%) of those who took placebo (fixed effects odds ratio 1.70, 95% CI 1.13–2.54, $P=0.01$). There was a slight trend for individual suicidal thoughts, attempts, and self-harm to occur more often in youths taking ADs than in those given placebo; however, none of these differences were statistically significant.

Finally, Olmer and colleagues [100] in a case-control study investigated the relationship between ADs and suicide attempts. Overall, 103 medical records of patients admitted after a suicide attempt (case group) were compared with 103 medical records of matched depressed patients admitted without suicide attempts (control group 1) and with 25 patients with and

without suicide attempts on separate hospitalizations (control group 2). As a result, no difference between cases and controls was reported.

31.8 Antidepressant Medications and Suicide Risk: Management and Treatment

Clinicians should be confident about depressive symptom improvement when an AD is initiated but simultaneously use cautions in the presence of suicide risk. In summary, they should:

1. Share with patients the assumption that the initial phase of AD treatment is a powerful indicator of the increased overall risk.
2. Carefully monitor patients during this starting time, in particular in the case of adolescents.
3. Warn patients and family members about the eventual worsening of depressive symptoms, as well as the emergence of suicidal ideation and self-harm.
4. Note any escalation—especially concerning suicidal ideation and self-harm—as a signal that the patient needs a rapid and systematic evaluation and treatment.
5. Advise patients that the interruption of AD drugs may also trigger a period of higher suicide risk justifying an intensified surveillance for a period of at least 4 weeks.

As previously anticipated and consistently with the aforementioned management indications, Isacsson and Rich [21] identified three major issues that could significantly guide to better treatment outcomes: (1) a careful reevaluation of the FDA warning in the light of the most recent findings; (2) a careful education of all health-care providers about the importance of aggressively treating depression, especially in youths and adolescents; and (3) an awareness about the higher risk of suicide of specific psychiatric conditions that should be closely monitored. These recommendations are necessary regardless of the type of AD treatment which has been provided.

However, it's also important to note that all medical treatments are associated with some risks, and AD drugs may be not excluded with this regard. As suggested, major depression is one of the major drivers of self-harm and suicidal behavior (it has been found in 87–92 % of suicide cases as reported by Angst and colleagues [101] and Hawton et al. [84]).

Therefore, in summary, clinicians should use vigilance for those patients who have been indicated as having a higher suicide risk, but in parallel they should also be careful to not a priori deny potentially effective drugs to some patients on the exclusive basis of unclear and controversial evidence.

31.9 Pharmacogenomics: A Future Prospective

Pharmacogenomics could lead to significant improvements of our current knowledge about AD treatment since it permits to create personalized treatments together with a better prediction of possible drug resistances.

For example, CYP2D6 is one of the most studied liver enzymes that may be related to psychiatric conditions and suicide risk [102]. Subjects with an increased number of CYP2D6 active genes, who are assumed to have a high enzyme activity in drug metabolism/elimination, seem to be more likely to die by suicide and to have a lifetime history of suicide attempts than those with a reduced number of CYP2D6 active genes [103–105]. CYP2D6 is involved in the metabolism of many psychoactive medications, such as AD medications. Thus, the effect of CYP2D6 on suicidal behavior can be partially due to drug therapeutic failure during AD treatment with CYP2D6 substrates and/or to differences in the central nervous system (CNS) regulation. Several studies found a poor response to AD drugs or early dropout from monotherapy treatment with CYP2D6 AD substrates in ultrarapid metabolizers [105–107]. CYP2C19 has also been found to be involved in the metabolism of SSRIs and TCAs; importantly, ultrarapid metabolizers have been identified as a high-risk group for poor treatment response and suicide risk [108]. Recently, for the first time a study

investigated the association between the CYP2D6- and CYP2C19-combined metabolic groups and the severity of the suicidal intent. The authors showed that a high CYP2D6-CYP2C19 metabolic capacity was related to increased severity of suicidal behavior. Consistently, most psychoactive drugs which were used for preventing or treating depressed and suicidal subjects are metabolized by CYP2D6 and CYP2C19 [102]. Unfortunately, studies investigating the individual adverse response to specific AD treatments and potentially providing genetic information for the best AD compounds in suicidal patients are yet to be carried out.

31.10 Conclusions: Major Limitations and Future Perspectives

Despite the large number of studies, no concluding evidence has been found, and the exact nature of the association between suicide rates and AD treatment remains controversial. However, a more careful and responsible AD use is absolutely required in clinical practice together with the need of adapting treatment strategies and closely monitoring the different investigated populations. At the same time, it is vital that primary care providers, who see and treat a substantial proportion of depressed patients, know that the risk posed by untreated depression—in terms of morbidity and mortality—has always been far greater than the very small risk associated with AD treatment [22]. The decision regarding the AD treatment should be balanced carefully assessing the suicide risk of patients as well as evaluating the whole clinical situation.

Some of the most relevant shortcomings of the abovementioned studies should be considered. For instance, observational studies may suffer from methodological limitations such as the achievement of inappropriate data and measures that may lead to questionable conclusions [109]. For example, projections of trends in rates of AD use or depression diagnoses that are based on historical trends are subject to error. Furthermore, methodological limitations may not allow this issue to be addressed adequately. The extremely low basal rate of suicide attempts and completed suicides needs to be interpreted as a limiting factor in cross-sectional studies analyzing the association between AD agent administration and suicidal risk. Meta-analytic approaches on larger samples seem to be only partially able to cover this gap [110].

Reliable tools helping clinicians in predicting how individual patients may differentially respond to particular AD medications are absolutely required [111]. Further additional studies together with deeper pharmacogenomic knowledge are also required, but to date cautions are needed when prescribing all AD drugs carefully weighing up all the potential risks and benefits related to the single cases.

References

1. World Health Organization. Preventing suicide: a global imperative. Luxemburg: WHO; 2014.
2. Mann JJ, Apter A, Bertolote J, Beautrais A, Currier D, Haas A, et al. Suicide prevention strategies: a systematic review. JAMA. 2005;294:2064–74.
3. Levi F, La Vecchia C, Lucchini F, Negri E, Saxena S, Maulik PK, et al. Trends in mortality from suicide, 1965–99. Acta Psychiatr Scand. 2003;108:341–9.
4. Tondo L, Baldessarini RJ, Hennen J, Minnai GP, Salis P, Scamonatti L, et al. Suicide attempts in major affective disorder patients with comorbid substance use disorders. J Clin Psychiatry. 1999;60 Suppl 2:63–9.
5. Tondo L, Isacsson G, Baldessarini RJ. Suicide in bipolar disorder: risk and prevention. CNS Drugs. 2003;17:491–511.
6. Roy A. Suicide. In: Sadock BJ, Sadock VA, editors. Kaplan and Sadock's comprehensive textbook of psychiatry, vol. 2. 7th ed. Philadelphia: Lippincott Willians and Wilkins; 2000. p. 2031–40.
7. American Psychiatric Association (APA). Practice guideline for the assessment and treatment of patients with suicidal behaviors. Am J Psychiatry. 2003;160(11 Suppl):1–60.
8. Harris EC, Barraclough B. Suicide as an outcome for mental disorders. A meta-analysis. Br J Psychiatry. 1997;170:205–28.
9. Cassano P, Fava M. Depression and public health: an overview. J Psychosom Res. 2002;53:849–57.
10. Koukopoulos A, Koukopoulos A. Agitated depression as a mixed state and the problem of melancholia. Psychiatr Clin N Am. 1999;22:547–64.
11. Akiskal HS, Benazzi F, Perugi G, Rihmer Z. Agitated "unipolar" depression re-conceptualized as a depres-

sive mixed state: implications for the antidepressant-suicide controversy. J Affect Disord. 2005;85: 245–58.
12. Maj M, Pirozzi R, Magliano L, Fiorillo A, Bartoli L. Agitated "unipolar" major depression: prevalence, phenomenology, and outcome. J Clin Psychiatry. 2006;67:712–9.
13. Arroll B, Elley CR, Fishman T, Goodyear-Smith FA, Kenealy T, Blashki G, et al. Antidepressants versus placebo for depression in primary care. Cochrane Database Syst Rev. 2009;(3):CD007954.
14. Gibbons RD, Brown CH, Hur K, Davis JM, Mann JJ. Suicidal thoughts and behavior with antidepressant treatment: reanalysis of the randomized placebo-controlled studies of fluoxetine and venlafaxine. Arch Gen Psychiatry. 2012;69(6):580–7.
15. Stone M, Laughren T, Jones TL, Levenson M, Holland PC, Hughes A, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. BMJ. 2009;339:b2880.
16. Friedman RA, Leon AC. Expanding the black box—depression, antidepressants, and the risk of suicide. N Engl J Med. 2007;356:2343–6.
17. Hall WD. How have the SSRI antidepressants affected suicide risk? Lancet. 2006;367:1959–62.
18. King RA, Riddle MA, Chappell PB, Hardin MT, Anderson GM, Lombroso P, et al. Emergence of self-destructive phenomena in children and adolescents during fluoxetine treatment. J Am Acad Child Adolesc Psychiatry. 1991;30:179–86.
19. Gordon MS, Melvin GA. Do antidepressants make children and adolescents suicidal? J Ped Child Health. 2014;50(11):847–54.
20. Hammad TA. Review and evaluation of clinical data. TGA. 2004. Available from: http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-10-TAB08-Hammads-Review.pdf. Accessed 13 Jul 2015.
21. Isacsson G, Rich CL. Antidepressant drugs and the risk of suicide in children and adolescents. Paediatr Drugs. 2014;16(2):115–22.
22. Friedman RA. Antidepressants' black-box warning – 10 years later. N Engl J Med. 2014;371(18):1666–8.
23. Laughren TP. Overview for December 13 meeting of Psychopharmacologic Drugs Advisory Committee (PDAC). 2006. www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-01-FDA.pdf. Accessed 6 Jul 2015.
24. Gøtzsche PC. Deadly medicines and organised crime: how big pharma has corrupted health care. London: Radcliffe Publishing; 2013.
25. Gibbons RD, Brown CH, Hur K. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am J Psychiatry. 2007;164:1356–63.
26. Stone MB. The FDA, warning on antidepressants and suicidality—why the controversy? N Engl J Med. 2014;371(18):1668–71.
27. Case BG. More data needed to interpret link between suicide and FDA warning on antidepressants. BMJ. 2014;349:g5616.
28. Lu CY, Zhang F, Lakoma MD, Madden JM, Rusinak D, Penfold RB, et al. Changes in antidepressant use by young people and suicidal behavior after FDA warnings and media coverage: quasi-experimental study. BMJ. 2014;348:g3596.
29. Libby AM, Orton HD, Valuck RJ. Persisting decline in depression treatment after FDA warnings. Arch Gen Psychiatry. 2009;66:633–9.
30. Mittal VM, Brown CH, Prior HJ, Marcus SC, Greenberg T. Trend of antidepressants prescriptions in the pedriatric population before and the FDA warning: a follow up study. Arch Pediatr. 2013;26(10): 1319–31.
31. Clarke G, Dickerson J, Gullion CM, DeBar LL. Trends in youth antidepressant dispensing and refill limits, 2000 through 2009. J Child Adolesc Psychopharmacol. 2012;22(1):11–20.
32. Reeves RR, Ladner ME. Antidepressant-induced suicidality: an update. CNS Neurosci Ther. 2010; 16(4):227–34.
33. Katz LY, Kozyrskyj AL, Prior HJ, Enns MW, Cox BJ, Sareen J. Effect of regulatory warnings on antidepressant prescription rates, use of health services and outcomes among children, adolescents and young adults. CMAJ. 2008;178(8):1005–11.
34. Wijlaars LP, Nazareth I, Petersen I. Trends in depression and antidepressant prescribing in children and adolescents: a cohort study in The Health Improvement Network (THIN). PLoS One. 2012;7(3):e33181.
35. Olfson M, Shaffer D, Marcus SC, Greenberg T. Relationship between antidepressant medication treatment and suicide in adolescents. Arch Gen Psychiatry. 2003;60:978–82.
36. Olfson M, Schoenbaum M. Link between FDA antidepressant warnings and increased suicide attempts in young people is questionable. BMJ. 2014;349: g5614.
37. Nardo JM. Impossible to draw meaningful conclusions from study of changes in antidepressant use after FDA warnings. BMJ. 2014;349:g5643.
38. Barber C, Azrael D, Miller M. Study findings on FDA antidepressant warnings and suicide attempts in young people: a false alarm? BMJ. 2014;349:g5645.
39. Moore TJ. Antidepressants increase, rather than decrease, risk of suicidal behaviours in younger patients. BMJ. 2014;349:g5626.
40. Lu CY, Simon G, Soumerai SB. Authors' reply to Olfson and Schoenbaum, Nardo, Bartlett, Moore, Case, Gøtzsche, and Barber and colleagues. BMJ. 2014;349:g5722.
41. Xiang Y, Zhao W, Xiang H, Smith GA. ED visits for drug-related poisoning in the United States. Am J Emerg Med. 2012;30:293–301.
42. Nock MK, Green JG, Hwang I, McLaughlin KA, Sampson NA, Zaslavsky AM, et al. Prevalence, correlates and treatment of lifetime suicidal behavior among adolescents: results from the National Comorbidity Survey Replication Adolescent Supplement. JAMA Psychiatr. 2013;70:300–10.
43. Bailly D. Antidepressant use in children and adolescents. Arch Pediatr. 2009;16(10):1415.

44. Leon AC, Solomon DA, Li C, Fiedorowicz JG, Coryell WH, Endicott J, et al. Antidepressants and risks of suicide and suicide attempts: a 27-year observational study. J Clin Psychiatry. 2011;72(5):580–6.
45. Isacsson G, Holmgren P, Ahlner J. Selective serotonin reuptake inhibitor antidepressants and the risk of suicide: a controlled forensic database study of 14,857 suicides. Acta Psychiatr Scand. 2005;111:286–90.
46. Centers for Disease Control and Prevention. Web-based Injury Statistics Query and Reporting System (WISQARS). 2003. www.cdc.gov/ncipc/wisqars. Accessed 6 Jul 2015.
47. California Department of Public Health, Safe and Active Communities Branch. http://epicenter.cdph.ca.gov. Accessed 13 Jul 2015.
48. Mosholder AD, Willy M. Suicidal adverse events in pediatric randomized, controlled clinical trials of antidepressant drugs are associated with active drug treatment: a meta-analysis. J Child Adolesc Psychopharmacol. 2006;16:25–32.
49. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry. 2006;63:332–9.
50. Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA. 2007;297(15):1683–96.
51. Wohlfarth TD, van Zwieten BJ, Lekkerkerker FJ, et al. Antidepressants use in children and adolescents and the risk of suicide. Eur Neuropsychopharmacol. 2006;16:79–83.
52. March JS, Klee BJ, Kremer CM. Treatment benefit and the risk of suicidality in multicenter, randomized, controlled trials of sertraline in children and adolescents. J Child Adolesc Psychopharmacol. 2006;16:91–102.
53. Kaizar EE, Greenhouse JB, Seltman H, Kelleher K. Do antidepressants cause suicidality in children? A Bayesian meta-analysis. Clin Trials. 2006;3:73–98.
54. Hammad TA, Mosholder AD. Suicide and antidepressants. Beware extrapolation from ecological data. BMJ. 2010;341:c6844.
55. Pamer C, Hammad TA, Yu T, Kaplan S, Rochester G, Governale L, et al. Changes in US antidepressant and antipsychotic prescription patterns during a period of FDA actions. Pharmacoepidemiol Drug Safe. 2010;19:158–74.
56. Centers for Disease Control and Prevention. Youth risk behavior surveillance system. Trends in the prevalence of suicide-related behaviours. National YRBS: 1997–2011. www.cdc.gov/healthyyouth/yrbs/pdf/us_suicide_trend_yrbs.pdf. Accessed 13 Jul 2015.
57. Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant prescription rates and rate of early adolescent suicide. Am J Psychiatry. 2006;163(11):1898–904.
58. Hall WD, Lucke J. How have the selective serotonin reuptake inhibitor antidepressants affected suicide mortality? Aust N Z J Psychiatr. 2006;40:941–50.
59. Søndergård L, Kvist K, Andersen PK, Kessing LV. Do antidepressants precipitate youth suicide? Eur Child Adolesc Psychiatry. 2006;5:232–40.
60. Simon GE, Savarino J. Suicide attempts among patients starting depression treatment with medications or psychotherapy. Am J Psychiatry. 2007;164:1029–34.
61. Leon AC, Demirtas H, Li C, Hedeker D. Two propensity score-based strategies for a three-decade observational study: investigating psychotropic medications and suicide risk. Stat Med. 2012;31(27):3255–60.
62. Kamat MA, Edgar L, Niblock P, McDowell C, Kelly CB. Association between antidepressant prescribing and suicide rates in OECD countries: an ecological study. Pharmacopsychiatry. 2014;47(1):18–21.
63. Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Tanskanen A, Haukka J. Antidepressants and the risk of suicide, attempted suicide, and overall mortality in a nationwide cohort. Arch Gen Psychiatry. 2006;63:1358–67.
64. Gusmão R, Quintão S, McDaid D, Arensman E, Van Audenhove C, Coffey C, et al. Antidepressant utilization and suicide in Europe: an ecological multinational study. PLoS One. 2013;8(6):e66455.
65. Leon AC, Marzuk PM, Tardiff K, Teres JJ. Paroxetine, other antidepressants, and youth suicide in New York City: 1993 through 1998. J Clin Psychiatry. 2004;65:915–8.
66. Leon AC, Marzuk PM, Tardiff K, Bucciarelli A, Markham, Piper T, et al. Antidepressants and youth suicide in New York City, 1999–2002. J Am Acad Child Adolesc Psychiatry. 2006;45:1054–8.
67. Singh VD, Lathrop SL. Youth suicide in New Mexico: a 26-year retrospective review. J Forensic Sci. 2008;53:703–8.
68. Cortes E, Cubano A, Lewis JE, Castellanos D. Antidepressants at autopsy in hispanic suicidal youth in Miami-Dade County. Florida J Forensic Sci. 2011;56:155–60.
69. Wasserman D, Wasserman C. The Oxford textbook of suicidology and suicide prevention. Oxford: Oxford University Press; 2011.
70. Gibbons RD, Hur K, Brown CH, Davis JM, Mann JJ. Benefits from antidepressants: synthesis of 6-week patient-level outcomes from double-blind placebo-controlled randomized trials of fluoxetine and venlafaxine. Arch Gen Psychiatry. 2012;69(6):572–9.
71. Erlangsen A, Conwell Y. Age-related response to redeemed antidepressants measured by completed suicide in older adults: a nationwide cohort study. Am J Geriatr Psychiatry. 2014;22(1):25–33.
72. Phillips JA, Nugent CN. Antidepressant use and method of suicide in the United States: variation by age and sex, 1998–2007. Arch Suicide Res. 2013;17(4):360–72.
73. Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. BMJ. 2005;330:385–8.

74. Fergusson D, Doucette S, Glass KC, Shapiro S, Healy D, Hebert P, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. BMJ. 2005;330(7488):396.
75. Shah A, Zhinchin G, Zarate-Escudero S, Somyaji M. The relationship between the prescription of psychotropic drugs and suicide rates in older people in England and Wales. Int J Soc Psychiatry. 2014; 60(1):83–8.
76. Brent D. Effective treatments for suicidal youth: pharmacological and psychosocial approaches. In: Wasserman D, Wasserman C, editors. The Oxford textbook of suicidology and suicide prevention. Oxford: Oxford University Press; 2011. p. 667–76.
77. Julious SA. Efficacy and suicidal risk for antidepressants in paediatric and adolescent patients. Stat Methods Med Res. 2013;22(2):190–218.
78. Hetrick SE, McKenzie JE, Merry SN. The use of SSRIs in children and adolescents. Curr Opin Psychiatr. 2010;23:53–7.
79. Henry A, Kisicki MD, Varley C. Efficacy and safety of antidepressant drug treatment in children and adolescents. Mol Psychiatry. 2012;17(12):1186–93.
80. Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN. Newer generation antidepressants for depressive disorders in children and adolescents. Cochrane Database Syst Rev. 2012;(11):CD004851.
81. Coupland C, Hill T, Morriss R, Arthur A, Moore M, Hippisley-Cox J. Antidepressant use and risk of suicide and attempted suicide/self-harm in people aged 20 to 64: cohort study using a primary care database. BMJ. 2015;350:h517.
82. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ. 2011;343:d4551.
83. Schneeweiss S, Patrick AR, Solomon DH, Mehta J, Dormuth C, Miller M, et al. Variation in the risk of suicide attempts and completed suicides by antidepressant agent in adults: a propensity score-adjusted analysis of 9 years' data. Arch Gen Psychiatry. 2010;67:497–506.
84. Hawton K, Bergen H, Simkin S, Cooper J, Waters K, Gunnell D, et al. Toxicity of antidepressants: rates of suicide relative to prescribing and non-fatal overdose. Br J Psychiatry. 2010;196:354–8.
85. Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet. 2009;373:746–58.
86. Watanabe N, Omori IM, Nakagawa A, Cipriani A, Barbui C, Churchill R, et al. Mirtazapine versus other antidepressive agents for depression. Cochrane Database Syst Rev. 2011;12:CD006528.
87. Garlow SJ, Kinkead B, Thase ME, Judd LL, Rush AJ, Yonkers KA, et al. Fluoxetine increases suicide ideation less than placebo during treatment of adults with minor depressive disorder. J Psychiatr Res. 2013; 47(9):1199–203.
88. Grunebaum MF, Keilp JG, Ellis SP, Sudol K, Bauer N, Burke AK, et al. SSRI versus bupropion effects on symptom clusters in suicidal depression: post hoc analysis of a randomized clinical trial. J Clin Psychiatry. 2013;74(9):872–9.
89. Makris GD, Reutfors J, Ösby U, Isacsson G, Frangakis C, Ekbom A, et al. Suicide seasonality and antidepressants: a register-based study in Sweden. Acta Psychiatr Scand. 2013;127(2):117–25.
90. Valenstein M, Kim HM, Ganoczy D, Eisenberg D, Pfeiffer PN, Downing K, et al. Antidepressant agents and suicide death among US Department of Veterans Affairs patients in depression treatment. J Clin Psychopharmacol. 2012;32(3):346–53.
91. Zisook S, Lesser IM, Lebowitz B, Rush AJ, Kallenberg G, Wisniewski SR, et al. Effect of antidepressant medication treatment on suicidal ideation and behavior in a randomized trial: an exploratory report from the Combining Medications to Enhance Depression Outcomes Study. J Clin Psychiatry. 2011;72(10):1322–32.
92. Perlis RH, Uher R, Perroud N, Fava M. Do suicidal thoughts or behaviors recur during a second antidepressant treatment trial? J Clin Psychiatry. 2012;73(11):1439–42.
93. Cooper WO, Callahan ST, Shintani A, Fuchs DC, Shelton RC, Dudley JA, et al. Antidepressants and suicide attempts in children. Pediatrics. 2014; 133(2):204–10.
94. Emslie GJ, Findling RL, Yeung PP, Kunz NR, Li Y. Venlafaxine ER for the treatment of pediatric subjects with depression: results of two placebo-controlled trials. J Am Acad Child Adolesc Psychiatry. 2007;46(4):479–88.
95. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published verses unpublished data. Lancet. 2004;363:1341–5.
96. Miller M, Pate V, Swanson SA, Azrael D, White A, Stürmer T. Antidepressant class, age, and the risk of deliberate self-harm: a propensity score matched cohort study of SSRI and SNRI users in the USA. CNS Drugs. 2014;28(1):79–88.
97. Hysinger EB, Callahan ST, Caples TL, Fuchs DC, Shelton R, Cooper WO. Suicidal behavior differs among early and late adolescents treated with antidepressant agents. Pediatrics. 2011;128(3): 447–54.
98. Cheung K, Aarts N, Noordam R, van Blijderveen JC, Sturkenboom MC, Ruiter R, et al. Antidepressant use and the risk of suicide: a population-based cohort study. J Affect Disord. 2015;174:479–84.
99. Dubicka B, Hadley S, Roberts C. Suicidal behaviour in youths with depression treated with new-generation antidepressants: meta-analysis. Br J Psychiatry. 2006;189:393–8.

100. Olmer A, Iancu I, Strous RD. Exposure to antidepressant medications and suicide attempts in adult depressed inpatients. J Nerv Ment Dis. 2012; 200(6):531–4.
101. Angst J, Angst F, Gerber-Werder R, Gamma A. Suicide in 406 mood-disorder patients with and without long-term medication: a 40 to 44 years' follow-up. Arch Suicide Res. 2005;9(3):279–300.
102. Peñas-Lledó E, Guillaume S, Naranjo MEG, Delgado A, Blasco-Fontecilla H, LLerena A. A combined high CYP2D6-CYP2C19 metabolic capacity is associated with the severity of suicide attempt as measured by objective circumstances. Pharmacogenomics. 2015;15(2):172–6.
103. Stingl JC, Viviani R. CYP2D6 in the brain: impact on suicidality. Clin Pharmacol Ther. 2011;89: 352–3.
104. Peñas-Lledó EM, Blasco-Fontecilla H, Dorado P, Vaquero-Lorenzo C, Baca-Garcia E, Llerena A. CYP2D6 and the severity of suicide attempts. Pharmacogenomics. 2012;13:179–84.
105. Peñas-Lledó EM, Trejo HD, Dorado P, Ortega A, Jung H, Alonso E, et al. CYP2D6 ultrarapid metabolism and early dropout from fluoxetine or amitriptyline monotherapy treatment in major depressive patients. Mol Psychiatry. 2013;18:8–9.
106. Lobello KW, Preskorn SH, Guico-Pabia CJ, Jiang Q, Paul J, Nichols AI, et al. Cytochrome P450 2D6 phenotype predicts antidepressant efficacy of venlafaxine: a secondary analysis of 4 studies in major depressive disorder. J Clin Psychiatry. 2010; 71:1482–7.
107. Tsai MH, Lin KM, Hsiao MC, Shen WW, Lu ML, Tang HS, et al. Genetic polymorphisms of cytochrome P450 enzymes influence metabolism of the antidepressant escitalopram and treatment response. Pharmacogenomics. 2010;11:537–46.
108. Sim SC, Kacevska M, Ingelman-Sundberg M. Pharmacogenomics of drug metabolizing enzymes: a recent update on clinical implications and endogenous effects. Pharmacogenomics. 2013;13: 1–11.
109. Spielmans GI, Jureidini J, Healy D, Purssey R. Inappropriate data and measures lead to questionable conclusions. JAMA Psychiatr. 2013;70(1): 121–2.
110. Moeller HJ. Pharmacological and other biological treatments of suicidal individuals. In: Wasserman D, Wasserman C, editors. The Oxford textbook of suicidology and suicide prevention. Oxford: Oxford University Press; 2011. p. 395–405.
111. Williams LM, Rush AJ, Koslow SH, Wisniewski SR, Cooper NJ, Nemeroff CB, et al. International study to predict optimized treatment for depression (iSPOT-D), a randomized clinical trial: rationale and protocol. Trials. 2011;12:4.