Published in final edited form as:

Pharmacogenomics. 2010 June ; 11(6): 793–807. doi:10.2217/pgs.10.64.

Pharmacogenomics of suicidal events

David Brent^{1,†}, Nadine Melhem¹, and Gustavo Turecki²

¹ Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Room 315 Bellefield Towers, Pittsburgh, PA 15213, USA

² McGill Group for Suicide Studies, Douglas Mental Health University Institute, 6875 LaSalle Boulevard, Verdun, Quebec H4H 1R3, Canada

Abstract

Pharmacogenomic studies of antidepressant treatment-emergent suicidal events in depressed patients report associations with polymorphisms in genes involved in transcription (*CREB1*), neuroprotection (*BDNF* and *NTRK2*), glutamatergic and noradrenergic neurotransmission (*GRIA3*, *GRIK2* and *ADRA2A*), the stress and inflammatory responses (*FKBP5* and *IL28RA*), and the synthesis of glycoproteins (*PAPLN*). Nearly all of the reported events in these studies were modest one-time increases in suicidal ideation. In 3231 unique subjects across six studies, 424 (13.1%) patients showed increases in suicidal ideation, eight (0.25%) attempted suicide and four (0.12%) completed suicide. Systems related to most of these genes have also been implicated in studies of suicidal behavior irrespective of treatment. Future pharmacogenomic studies should target events that are clinically significant, related clinical phenotypes of response and medication side effects, and biological pathways that are involved in these outcomes in order to improve treatment approaches.

Keywords

antidepressant; depression; genetics; pharmacogenomics; suicidal ideation; suicide; treatment

For nearly two decades, there has been concern that selective serotonin re-uptake inhibitors (SSRIs) and other antidepressants may, paradoxically, result in an increased risk for suicidal ideation and behavior in some depressed patients [1–3]. An analysis of all clinical trials registered with the US FDA found a twofold increase in suicidal ideation and behavior only in those under the age of 25 years, with a protective effect against suicidal events in those aged 40 years and older [4]. The majority of pharmacoepidemiologic studies across the lifespan find that the use of SSRIs is inversely related to the rate of suicide [5–9]. Nevertheless, concerns about the association between anti-depressants and suicidal events (defined as new-onset or worsening suicidal ideation or behavior [10]) has made practitioners less likely to prescribe antidepressants, especially for the young [5,11]. Therefore, the ability to identify, *a priori*, which depressed individuals exposed to

[†]Author for correspondence: Tel.: +1 412 246 5596, Fax: +1 412 246 5344, brentda@upmc.edu.

For reprint orders, please contact: reprints@futuremedicine.com

Financial & competing interests disclosures

This work was supported by a NARSAD Distinguished Investigator Award (David Brent, MD); NIMH grants MH61835, MH56612 (David Brent, MD); MH77930 (Nadine Melhem, PhD); and CIHR#151060 (Gustavo Turecki, MD, PhD). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

antidepressants are most likely to become suicidal could be very useful in clinical decision-making.

Those depressed patients who experience suicidal events are more likely to have greater clinical depressive severity, current suicidal ideation and past attempts, comorbid substance use, impulsive–aggressive traits, and greater exposure to early and current psychosocial stress [12–18]. In addition, depressed patients who experience suicidal events show a less vigorous response to treatment, are more likely to have received adjunctive treatment for anxiety or sleep difficulties, and may be more likely to experience certain side effects of antidepressants, such as activation and akathisia [13–19]. These clinical indicators are generally associated with greater severity and clinical complexity, and are not specifically predictive of suicidal outcomes. Pharmacogenomics, for example, may improve the identification of patients most likely to experience a suicidal event, above and beyond those identified via clinical predictors, and may help to more sharply define clinical phenotypes associated with a lack of response and treatment-emergent suicidal events [20].

In this article, we first review the extant literature on the pharmacogenomics of suicidal events in antidepressant studies of depressed patients, summarize the methodological issues involved in such studies and make recommendations for further research. In total, we summarize six reports on the pharmacogenomics of suicidal events: three studies reported from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study [13,18,21]; and one report each from the European Genome-based Therapeutic Drugs for Depression (GENDEP) study [14], the Munich Antidepressant Response Signature (MARS) project [22], and the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) study [23].

Summary of extant studies

Table 1 summarizes the studies described in the following sections.

STAR*D

Study 1—Perlis *et al.* examined the relationship between polymorphisms in the cyclic adenosine response-element binding protein (*CREB1*) and treatment-emergent suicidal ideation (TESI) in 1447 participants in the STAR*D study who were treated with citalopram [13]. Participants in the STAR*D study had unipolar depression without a comorbid eating disorder, psychosis or substance dependence. Participants with baseline suicidal ideation were excluded from these analyses. *CREB1* was selected for study because of its putative role in the action of anti-depressants, reported changes in *CREB1* gene expression in postmortem studies of suicide and the association of *CREB1* polymorphisms with anger expression in depressed males [24–27].

Phenotype: The phenotype TESI was defined as a Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) item-12 score of two or more at any post-baseline visit in those whose baseline score was a 0 or 1 (see Box 1 for anchor points for this item) [28]. TESI was correlated with a history of previous suicide attempts, feelings of hopelessness and more severe depression at baseline, as well as with adjunctive sedative or hypnotic treatment. Among the 539 males included in the final genetic analyses, 54 (10.0%) experienced TESI, of whom only one (0.18%) made a suicide attempt.

Box 1

Suicidal items from the Quick Inventory of Depressive Symptoms

- 0: I do not think of suicide or death

- 1: I feel life is empty or wonder if it is worth living
- 2: I think of suicide and death several times a week for several minutes
- 3: I think of suicide or death several times a day in some detail, or have actually tried to take my life

Genes studied: The genetic analyses focused exclusively on the *CREB1* gene. A total of 44 SNPs were tested, and based on HapMap information, five tagged SNPs were selected to capture the genetic variation in all exonic or putative promoter regions.

Findings: For the entire sample, there was no association between TESI and any *CREB1* SNP. However, among the 539 men in the study, TESI was associated with *CREB1* rs7569963 and rs4675690; this remained true when the sample was restricted to only Caucasian participants. This association was statistically significant only for events that occurred within the first 30 days of treatment. A Kaplan–Meier analysis showed an additive effect of the rs4675690 T allele with respect to earlier time to suicidal event. These analyses were repeated, and the results persisted after controlling for each of three covariates: baseline hopelessness, depression severity and use of a sedative or hypnotic during treatment. There was no relationship between these polymorphisms and either suicidal ideation at intake, or a past history of a suicide attempt. Haplotype analyses found an association between TESI and two of the eight *CREB1* haplotypes.

Study 2—Laje *et al.* reported on TESI in 1862 participants in the STAR*D sample [18]. This sample was, for the most part, clinically representative of STAR*D as a whole.

Phenotype: The phenotype for TESI was based on the responses to item 12 from the QIDS self-report scale (QIDS-S). Those considered positive for emergent ideation scored 0 at baseline and, subsequently, had a score of 1 or more. The control group had to have zeros on the QIDS-S through the treatment period. TESI was reported in 120 out of 1862 participants (6.4%), with one (0.05%) making a suicide attempt.

Genes studied: A total of 68 candidate genes were surveyed that represented five pathways relevant to anti-depressant action: serotonin (20 genes), glutamate (16 genes), dopamine (three genes), norepinephrine (four genes) and neurotrophins (four genes), along with other selected genes (21 genes). Within these 68 genes, 768 SNPs were examined. The program LDSelect was used to choose an optimal set of SNPs, spanning the coding region and up to 2 kbp of the flanking sequence [29].

Findings: Two markers showed evidence of an association with an experiment-wise p-value of less than 0.05: glutamate receptor, ionotropic, kainite 2 (*GRIK2*; rs2518224) was associated with TESI for the genotypic test (CC genotype, odds ratio [OR]: 8.2; nominal $p = 2.43 \times 10^{-5}$; experiment-wise $p < 0.003$). Furthermore, the glutamate receptor ionotropic AMPA 3 (*GRIA3*; rs4825476) was associated with TESI in the allelic test (G allele, OR: 1.9; nominal $p = 7.84 \times 10^{-5}$; experiment-wise $p < 0.01$). Kaplan–Meier analyses were not conducted, but 69% of events occurred within the first 3 weeks of the trial. While no haplotype analyses were reported, there was an additive risk for TESI in individuals who had both the *GRIA3* rs4825476G allele and the *GRIK2* rs2518224CC genotype (OR: 15.0). The one suicide attempter, although never having suicidal ideation, had risk alleles from both genes.

Subsequent logistic regressions were conducted to control for demographic (race) and clinical variables (maximum citalopram dose and remission). For both men and women,

there was a significant association of TESI with both the *GRIK2* rs25184224CC genotype and the *GRIA3* rs4825476G allele. There was no relationship between these two risk alleles and a past history of suicide attempt, past suicidal ideation or suicidal ideation at baseline prior to treatment. Furthermore, the analyses indicated that there was no evidence of population stratification.

The authors tested the robustness of the findings by varying the phenotypic definition of TESI. When using the same definition on the clinician (QIDS-C) rather than self-report (QIDS-S) version of the QIDS, associations were demonstrated at the same two genes, but with different SNPs. Those who met criteria on both the QIDS-C and QIDS-S showed a stronger association with the risk alleles reported above. Furthermore, those participants with a TESI that moved from 0 to 1 and those whose scores increased by more than 1 were compared; these two subgroups showed similar findings.

Study 3—In a separate report, Laje *et al.* also conducted a genome-wide association study (GWAS) with respect to TESI [21] on a subsample of the STAR*D participants reported earlier [18,21]. A total of 90 cases (those with TESI) and 90 age-, ethnicity- and sex-matched controls were compared. Controls had to have a QIDS-C of 10 or more, adherence to medication, no history of suicide attempts or ideation and recurrent depression. Once risk markers were identified, an additional 94 participants meeting control criteria were genotyped for the risk markers and added to the control group.

Phenotype: The clinical phenotype of TESI was the same as that described earlier by Laje and colleagues [18].

Genes studied: Genotyping was conducted using the Illumina Human-1M Beadchip® (Illumina Inc., CA, USA) with a density of 109,365 SNPs. Risk markers identified in the case-control study were genotyped in the whole STAR*D sample (n = 1915) on whom DNA was obtained, using the TaqMan (Applied Biosystems, Inc., CA, USA) assays.

Findings: One marker, the rs11628713 of the papilin (*PAPLN*) gene, was associated with TESI at a p-value of 6.2×10^{-7} (OR: 4.9; experiment-wise p = 0.01). The C allele was over-represented in the TESI group. One marker, rs10903034 on the IL-28 α -receptor (*IL28RA*) gene was associated with TESI at an overall p-value of 3.02×10^{-6} and an experiment-wide p-value of 0.06 (OR: 2.7). The associations between both markers and TESI were examined in the entire STAR*D, and the findings were consistent for both the *PAPLN* (p = 0.001) and the *IL28RA* markers (p = 0.034). Conversely, the association between the *GRIA3* reported in an earlier study on the entire STAR*D genotyped sample [18] was examined in this subsample of 274 participants. The exact same *GRIA3* SNP was not included in the SNP array used for the GWAS, but the marker genotyped in this study (rs5911588) with the highest r^2 (of 0.46) with the previous reported risk marker on the *GRIA3* gene (rs4825476) showed an association with TESI (p = 0.0004). The cases and controls were similar with respect to most variables. Similar to the larger STAR*D sample, those who experienced TESI were less likely to experience remission and had received higher doses of citalopram; adjustment for these two variables did not change the results. Formal haplotype analyses were not conducted, but the highest risk for developing TESI was observed when all risk alleles/genotypes were present (*GRIA3G*; *GRIK2CC*, *PAPLNCC* and *IL28RAAA*). These results were not attributable to population stratification.

GENDEP

Perroud and colleagues conducted a pharmacogenetic study of TESI and treatment worsening onset of suicidal ideation (TWOSI) in the GENDEP study [14]. A total of 796

adult unipolar depressed patients treated with either escitalopram or nortryptiline with flexible dosing were genotyped. Participants who could not tolerate or did not respond to one drug were switched to the other, and events that occurred under either drug condition were counted in these analyses.

Phenotype—Emergent or worsening suicidal ideation was assessed using three items: item 3 from the 17-item Hamilton Depression Rating Scale (HAM-D-3), item 10 from the Montgomery–Asberg Depression Rating Scale (MADRS-10), and item 9 from the self-reported 21-item Beck Depression Inventory (BDI-9). A composite score was constructed using Item Response Theory [30]. TESI and TWOSI were found to share common risk factors in previous analyses [31] and were combined into one ‘case’ group, defined as having at least a 0.5 standard deviation increase on the composite scale from baseline and at least 1 standard deviation above the lowest possible score. This corresponds to 1 or more on the BDI-9, 1 or more on the HAM-D-3 and 2 or more on the MADRS-10. Out of 796 participants, 254 (31.9%) had TESI or TWOSI. Out of these, three (0.38%) engaged in suicidal behavior – two attempts and one completed suicide.

Genetics—A total of 123 SNPs were tested in nine candidate genes, related to serotonergic neurotransmission (serotonin 1A receptor [*HRT1A*], serotonin 2A receptor [*HRT2A*], tryptophan hydroxylase 1 [*TPH1*], tryptophan hydroxylase 2 [*TPH2*] and serotonin transporter [*SCL6A4*]), nor-adrenergic neurotransmission (α -2 adrenergic receptor [*ADRA2A*] and norepinephrine transporter [*SCL6A2*]) and neurotrophic functions (brain-derived neurotrophic factor [*BDNF*] and neurotrophic tyrosine kinase receptor type 2 [*NTRK2*]). SNPs were selected using the SNPTagger program and HapMap data on the Centre d’Etude du Polymorphisme Humain (CEPH) Project in Utah (CEU) population with European ancestry. SNPs chosen were required to have a minor allele frequency of 5% or greater, and a pair-wise linkage disequilibrium of r^2 of 0.8 or more SNPs were genotyped using the SNPLex method.

Findings—Within the entire sample, that is, in participants treated with either citalopram or nortryptiline, the *BDNF* gene rs962369 was associated with TESI/TWOSI ($p = 0.0015$; corrected $p = 0.04$). Haplotype analyses identified a block of all polymorphisms that were in strong linkage disequilibrium, which was significant with an experiment-wide p -value of 0.04. Two *NTRK2* haplotypes were identified; one that increased, and one that decreased suicidal ideation; both showed experiment-wise p -values of less than 0.05. There was an interaction between the two functional *BDNF* polymorphisms (rs6265 and GT [n] repeat) and the three SNPs in the *NTRK2* in the 3’ region ($p = 0.00026$; corrected $p = 0.01$).

No association was found between any markers and TESI/TWOSI in those treated with escitalopram. For those treated with nortryptiline, rs11195419 in the *ADRA2A* gene was associated with increased suicidal ideation ($p = 0.007$), but this did not survive correction for multiple tests. There was a significant gene by drug interaction (uncorrected $p < 0.0001$); the *ADRA2A* rs11195419A allele conveyed increased risk for TESI/TWOSI in those treated with nortryptiline. In a previous report on this sample, males were found to be much more likely to experience TESI/TWOSI if they were treated with nortryptiline [31]. In this study, there was gender-by-gene interaction for those taking nortryptiline; males with the *ADRA2A* rs11195419A allele were much more likely to have new-onset or worsening ideation than females. All results persisted after control for baseline severity of depression, change in observed mood over the course of treatment and previous history of suicide attempts. However, a history of suicide attempts was also related to these markers. A strong association with TESI/TWOSI was found in those aged 25–64 years ($p = 0.00055$ for *BDNF* rs962369); the other two age strata were too small to conduct meaningful tests of association.

MARS

Menke *et al.* [22] reported a replication of the study of Laje *et al.* in a brief report [18]. The participants comprised 397 depressed inpatients participating in the MARS project who were treated with a wide variety of antidepressants prescribed at the discretion of their physicians.

Phenotype—The phenotype was defined as a score of 1 or more on item 3 on the HAM-D-3 sometime during the trial, and a 0 on this item at baseline. The controls were all individuals who showed no increase in baseline suicidality on this item; a subgroup of these controls was also examined that had scores of 0 throughout the trial. The findings were stronger when the stricter definition of the control group was applied, and herein, we review those results. Out of 397 participants, 32 (8.1%) experienced TESI: no attempts, but three suicide completions (0.08%) were reported.

Genetics—In total, 112 SNPs in the *GRIK2* gene and 17 SNPs in the *GRIA3* gene were genotyped using Illumina custom arrays.

Findings—The rs4825476 marker within the *GRIA3* gene, which was associated with TESI in the STAR*D study, was also associated with TESI in this sample, but with a different risk allele (A vs G in STAR*D; $p = 0.04$). The SNP within the *GRIK2* gene (rs2518224) that was associated with TESI in the STAR*D study was not associated with TESI in this sample ($p = 0.86$). There were significant associations with other *GRIK2* SNPs: rs2852618 ($p = 0.005$), rs954765 ($p = 0.007$) and rs2782900 ($p = 0.007$). The three suicide victims all carried risk alleles from both genes.

TORDIA

In the only report of the pharmacogenomics of suicidal events in depressed adolescents, Brent *et al.* reported on the relationship between selected genetic markers and both response and suicidal events in a subsample of the TORDIA study [23]. The sample consisted of 176 participants, out of a total of 292 who were eligible. All the participants were aged 12–18 years, and had treatment-resistant unipolar depression that had not responded to an adequate trial with an SSRI. Participants were randomized to either switch to another SSRI (paroxetine, citalopram or fluoxetine), switch to venlafaxine, or switch to either of these two medication conditions with additional cognitive behavioral therapy (CBT).

Phenotype—Suicidal events were defined as new-onset or worsening suicidal ideation or behavior. All events were decided by consensus. For the first half of the study, events were rated by spontaneous report as was commonly done in previous clinical trials [32]. Midway through the study, after the FDA black box warning on antidepressants, weekly systematic monitoring for suicidal events was implemented. For the second half of the study, an event was coded if there was a 1-point increase on the Brief Suicide Severity Rating Scale (B-SSRS) [10], for which both ideation and behavior are rated on a 1–5 scale. Results were similar using spontaneously versus systematically assessed events; however, the majority (75%) of events in this study were detected by systematic assessment [15]. Out of 176 participants, 18 experienced TESI (10.2%), of whom four (2.2%) attempted suicide.

Genetics—A total of 21 polymorphisms were genotyped in 12 genes involving serotonergic (serotonin receptors [*HRT1A* and *HRT2A*], *TPHI* and *SLC6A4*), noradrenergic (norepinephrine transporter [*SLC6A2*] and β -1 norepinephrine receptor [*ADRB1*]), dopaminergic (dopamine transporter [*SLC6A3*]) or glutamatergic neurotransmission (*GRIA3* and *GRIK2*); monoamine metabolism (*MAOA*), neurotrophic functions (*BDNF*), or the hypothalamic–pituitary–adrenal axis (FK506-binding protein 5 [*FKBP5*]). These genes were

selected because they have been shown to be involved in the mechanism of action of antidepressants, the etiology of depression, or had been reported in previous pharmacogenetic studies as being related to either treatment response or suicidal events.

Findings—There were significant associations between the *FKBP5* rs1360780 T and rs3800373 G alleles and suicidal events, even after controlling for relevant treatment (medication or medication plus CBT) and clinical variables (family conflict, use of trazodone or family conflict by genotype; ORs 59.3 and 36.8, respectively, $p = 0.0007$; corrected $p = 0.025$). These two SNPs were in very tight linkage disequilibrium ($r = 0.91$). Genotypic analyses showed that the effect was mainly due to the homozygous TT and GG genotypes, respectively, which were both associated with a greater hazard and earlier time to an event (corrected p -values of 0.006 and 0.016, respectively). These genotypes were unassociated with a history of nonsuicidal self-injury, current suicidal ideation or history of a past attempt. Although suicidal events were more common in those who did not respond to treatment (21.9 vs 4.4%; $p = 0.001$), there were no significant associations between any of the genetic markers and treatment response.

Discussion

One might be justified in asking whether a review of the pharmacogenomics of treatment-emergent suicidal events is worthwhile, given that there are only six extant studies, with substantial heterogeneity in the defined phenotype. We believe that, while no firm scientific conclusions can be drawn from the reported data, there are important lessons to be learned from these studies that can help to design more useful and definitive pharmacogenomic studies of anti-depressant outcomes in the future. Paramount among these methodological issues is the definition of the phenotype of treatment-related suicidal events.

Definition of the phenotype of treatment-related suicidal events

Heterogeneity of definitions of suicidal events across studies—Among the six studies reviewed earlier, there were five different definitions of cases and of controls, which varied by assessment instrument, source (self-report, interview or both), required baseline level of suicidal ideation, and severity of required change in ideation. This makes cross-study comparisons very difficult. For example, the definition used by Perlis *et al.* classified controls as having a 0 (no ideation) or 1 (feeling life is empty or wondering if life is worth living) on the QIDS-C at baseline, and required a change to at least a 2 (thinking of suicide or death several times a week for several minutes) in order to be considered a case (see Box 1) [13]. By contrast, Laje *et al.* considered a transition from a 0 to a 1 on the self-report version of the same scale to be ‘emergent ideation’ [18]. Thus, a case in the Laje *et al.* study [18] would have been considered a control in the Perlis *et al.* study [13]. Moreover, information obtained about suicidal ideation from self-report questionnaires often differs from that obtained by interview [33]. The GENDEP study was notable insofar as it developed a measure of suicidal events that integrated self-report and interview data [14,31]. The frequency of suicidal events varied greatly across studies from 6.4% in the STAR*D study to 31.9% in the GENDEP study [14,18].

Three studies tested the extent to which findings are robust to variation in the definition of the case or control phenotype. The Laje *et al.* study showed that results were mostly convergent, regardless of whether the definition was based on self-report, interview or both [18]. In GENDEP, it was demonstrated that the results for TESI and TWOSI were similar [14,31]. Menke *et al.* found that results were stronger if controls had 0 on ideation, rather than simply no increase from baseline [22].

Clinical salience of suicidal events—The vast majority of suicidal events in these studies involved increases in suicidal ideation, rather than actual suicidal behavior (461 out of 469 cases [99.8%]). For some studies, a participant could be declared to have a suicidal event if an increase from no ideation to a passive death wish was reported on one occasion. This might be a cause for clinical concern but would not cause most clinicians to modify their treatment approach. For pharmacogenomic results to be clinically relevant, genetic variants should help identify patients for whom the predicted suicidal event would lead the clinician to change treatment strategies.

Family genetic and neurobiological investigations consistently show that the risk factors for suicidal ideation and for actual suicidal behavior are different [34–36]. The familial transmission of suicidal ideation is mediated by the familial transmission of depression, but the transmission of actual suicidal attempts is mediated by the transmission of impulsive aggression [35,37,38]. Altered central serotonin metabolism, whether studied by postmortem receptor binding, PET studies or direct measurement of serotonin function in living patients, is associated with suicidal behavior, rather than ideation and depression *per se* [36]. Therefore, it goes against what is known about the neurobiology of suicidal behavior to expect that the same biological process will underlie TESI (occurring without suicidal behavior) and treatment-emergent suicidal behavior, unless, in the context of a clinical trial, an increase in suicidal ideation triggers a therapeutic intervention that prevents the occurrence of suicidal behavior. Under these circumstances, research participants who show increases in ideation are similar to those who actually make a suicide attempt [39,40].

Relationship of suicidal events to other treatment-related phenotype—Several studies have shown that suicidal ideation and events occur in those who show a less vigorous response to treatment as well as in those who receive hypnotics or benzodiazepines [13,15,16,19]. However, the reported associations between genetic markers and suicidal outcomes persisted after controlling for response, remission, variations in antidepressant dose and the use of hypnotic drugs or antianxiety agents [13,14,18,21,23], thus supporting a specific association between treatment and suicidal events, rather than an indirect relationship mediated by other clinical phenomena or variations in treatment.

Investigators have hypothesized that treatment-related suicidal events may be mediated by medication side effects, such as activation, disinhibition, akathisia or mania [16,17,19,24,41,42], but no pharmacogenomic studies have reported on side effects and their relationship to both suicidal outcomes and risk genes. Also untested is the hypothesis that suicide events may be attributable to nonadherence, and subsequent withdrawal effects, especially in medications with short half-lives [43]. Pharmacogenomic studies of treatment response show that the relationship between genetic variation and response is moderated by antidepressant concentration [44,45]. Furthermore, genetics variants in the *CYP26* gene associated with ultrarapid metabolism have been reported to be over-represented in suicide completers and in those with treatment-resistant depression [46,47]. Yet, to our knowledge, neither the role of antidepressant exposure nor that of genetic variants in *CYP* genes have been examined in pharmacogenomic studies of suicidal events.

Relationship of suicidal events to other clinical phenotypes of suicidal behavior—Three studies tried, and failed, to find an association between genetic markers and either current intake ideation or past attempt, but it is unclear whether these studies had adequate power to accept the null hypothesis [13,18,23]. By contrast, in the GENDEP study, the genetic markers for treatment-emergent/worsening ideation were also associated with a history of past attempt [14]. Several of the studies examined many of the related clinical phenotypes and adjusted for these (e.g., depression severity, past attempt and hopelessness) as part of their analytic plan [13,14,18,21,23]. However, other clinical phenotypes, such as

anger, irritability and or impulsive aggression, that may be endophenotypes for suicidal behavior and have been reported to be associated with some of these risk genes were not assessed [24,38,48,49].

Are these suicidal events really treatment emergent?—None of these pharmacogenomic studies of suicidal events were placebo controlled. The only way to definitively show that a genetic marker is associated with treatment-emergent suicidal events is to demonstrate a genotype by treatment interaction in a placebo-controlled trial. This approach, while ideal, may make recruitment for pharmacogenomic studies more difficult, and might preclude studying patients who are at high risk for suicidal events.

Suicidal events that occur close to the initiation of treatment are more likely to be treatment emergent, since they follow the temporal pattern of suicidal events observed in placebo-controlled trials [16]. Consistent with this view, two studies found markers that predicted early onset of events [13,23]. In the other studies, the occurrence of the majority of events in the first 3–6 weeks of the trial is also consistent with these events being treatment emergent [14,18,21,22].

Common & distinct findings between genetic studies of suicidal behavior & pharmacogenomic studies of suicidal events—The genes associated with suicidal events in pharmacogenomic studies have often been implicated in studies of suicidal behavior or related phenotypes. While the timing of events suggests that they are treatment specific, these pharmacogenomic studies seem to be identifying individuals prone to suicidal behavior, regardless of treatment.

Polymorphisms in the *CREB1* gene have been shown to predict suicidal events in depressed males treated with citalopram. This gene is involved in antidepressant response [50], shows altered expression and phosphorylation in postmortem studies of suicide victims [25–27] and has been associated with altered anger expression in depressed men [24]. The Perlis *et al.* study did not find an association between *CREB1* and past suicide attempts, but this might be explained by its exclusion of all participants with baseline suicidal ideation from these analyses [13].

The GENDEP study found an association between polymorphisms in *BDNF* and a *BDNF* by *NTRK2* interaction with respect to suicidal events [14], as hypothesized several years ago by Tsai [51]. In the GENDEP study, these suicide risk genes were also related to a history of past suicide attempt. *BDNF* is implicated in the etiology of depression and in the action of anti-depressants, and altered expression of *BDNF* has been found in postmortem studies of suicides [52]. The Val66Met polymorphism was among those associated in suicidal events in the GENDEP study, and has also been shown to be related to suicide attempts in depressed and bipolar patients, patients with lower serotonin transporter availability and patients with greater impulsivity [53–56]. *NTRK2* is a receptor for *BDNF*. A relationship between *NTRK2* and suicidal behavior is also supported by postmortem and association studies [52,57,58].

The GENDEP study also advanced and confirmed an *a priori* hypothesis that polymorphisms in the *ADRA2A* would be associated with suicidal events in those treated with nortryptiline. While this finding appears to be treatment specific, increased numbers of α -2 receptors and mRNA expression has also been reported in suicide victims [59]. Furthermore, the *ADRA2A* polymorphisms found in this study are in linkage disequilibrium with other polymorphisms that have been associated with susceptibility to suicide completion and to impulsivity and irritability [60].

The STAR*D study found a relationship between polymorphisms in glutamatergic receptors and the occurrence of suicidal events. Both the *GRIK2* and *GRIA3* genes encode for ionotropic glutamate receptors, which have been implicated in the etiology of depression and in antidepressant response [61–63]. Ketamine, which is an agonist for NMDA, an ionotropic glutamate receptor, has recently been shown in open trials to reduce suicidal ideation and depressive symptoms in treatment-resistant depressives [64]. Both postmortem and association studies have implicated glutamatergic genes in suicide and suicidal behavior [65].

The STAR*D study also identified two other possible risk genes associated with suicidal events through a GWAS. *PAPLN* encodes a proteoglycan-like sulfated glycoprotein known as papilin; the implications of which are unclear in humans, or even in animal models of depression. The *IL28RA* gene encodes a class II cytokine receptor, which has not been studied in relationship to depression. Depression is accompanied by elevated levels of cytokines, and immunotherapy with IL-2 or IFN- α precipitates depression that can be attenuated with antidepressant treatment [66,67]. Higher levels of cerebrospinal fluid IL-6 have been associated with violent suicide attempts [68], with mixed findings regarding associations between other cytokine genes and suicidal behavior [69,70].

The TORDIA study found an association between the *FKBP5* gene and suicidal events in depressed adolescents [23]. The *FKBP5* gene encodes for a protein that causes the glucocorticoid receptor to be subsensitive to feedback from circulating cortisol, thus resulting in increased and prolonged cortisol response to stress [71–73]. The risk alleles found in TORDIA encode for a variant that results in greater transcription, and glucocorticoid receptor sub-sensitivity [71–73], parallel with similar alterations in the hypothalamic–pituitary–adrenal axis predicting future suicidal behavior [74]. A recent study in African–Americans found a strong association between the complementary *FKBP5* alleles and risk for suicide attempt [75]. Other studies have found that this variant is associated with increased risk for major depression, post-traumatic stress disorder symptoms in the face of maltreatment, increased number of depressive episodes and more rapid response to antidepressants in adults [20,76–78].

Thus, the findings of an association between suicide events and genetic variations in *CREB1*, *BDNF*, *NTRK2*, α -2 adrenoreceptors glutamatergic receptors and *FKBP5* are most consistent with a general increased genetic predisposition to suicidal behavior. These findings do not rule out some treatment-specific effect, as was demonstrated in the role of α -2 adrenoreceptor polymorphisms in predicting suicidal events exclusively in those treated with nortryptiline. However, there are other genes that have shown relatively consistent associations with suicidal behavior, such as *5HTTLPR*, *HTR1A*, *HTR2A* and *TPH1* [57]. While some of these genes have been implicated in the pharmacogenomics of treatment response or development of other side effects, none have been reported to be associated with treatment-emergent suicidal events [20,74,79,80].

Moderation by age & sex—A meta-analysis of placebo-controlled, anti-depressant trials shows an antidepressant-associated increase in suicidal ideation and behavior that is statistically greater only in people under the age of 25 years [4]. This does not mean that an increase in suicidal ideation cannot occur in older individuals, but that it is less common, and may be a different phenomenon from that observed in younger samples. Despite these well-known results, only one pharmacogenomic study attempted to examine differences in genetic associations by age, and that study was underpowered to do so [14]. Response to serotonergic versus noradrenergic antidepressants and risk markers thereof vary by age. Studies should be powered to test the possibility that age may moderate the relationship between genes and treatment-emergent events [81,82].

Three of these studies examined moderation of genetic effects by sex. Perlis *et al.*, acting on previous findings of a greater expression of depression in men versus women associated with *CREBI* [24], examined whether polymorphisms in the same gene would predict TESI only in men [13]. In the GENDEP study, an observation that men were particularly vulnerable to treatment-related suicidal events when treated with nortryptiline led investigators to test for an interaction between genotype and sex in those treated with nortryptiline [14,31].

Previous or current adversity—There is a strong relationship between stress, genetic vulnerability and both suicidal ideation and attempts [79,83], but only one study controlled for the effect of current stress [23]. A history of abuse has been shown to increase the risk for suicidal behavior and also to moderate the response to either medication or psychotherapy [39,84–86]. The effects of early childhood adversity and current stress may cause changes in serotonergic functioning, and interact with genetic variants of *BDNF* and *FKBP5* to increase the risk of depression, post-traumatic stress disorder and suicide attempts [75,76,87,88].

Genetic strategy—All studies included in this article used a case–control, population-based, association design and focused exclusively on genetic variation. Whether using a focused candidate-gene [13,14,18,22,23] or a genome-wide [21] approach, all studies used standard genetic methodology and genotyping procedures. The studies using candidate gene approaches based their choice of genes primarily on neurotransmitter systems and related regulatory factors. Despite findings showing a relationship between variations in drug metabolism and both suicide and treatment nonresponse, none of the studies reviewed here investigated genes that may be associated with or predict different metabolic responses to antidepressant treatment [46,47].

Proteomic approaches have been suggested as a method for identifying biomarkers for disease and for treatment response. Cerebrospinal fluid proteomics have identified proteins uniquely associated with depressed suicide attempters [89,90]. Animal models of depression have also been employed to identify proteins associated with antidepressant treatment and with depression [91]. The identification of proteins that are uniquely associated with antidepressant treatment response could help identify genes that, while not necessarily associated with the pathophysiology of the disorder, might predict individual differences in response to antidepressants.

Studies of gene expression are another promising approach that has been used to identify some of the genes studied in these association studies, namely, *CREBI*, *BDNF* and *NTRK2*, and has also been used to identify networks and classes of genes that may be involved in the pathophysiology of suicidal behavior [92,93]. Future approaches should include, in addition to methods assessing genetic variability, markers of gene function and regulation. More specifically, studies will be enhanced by incorporating gene-expression assays, other comprehensive mRNA studies or studies of miRNA changes associated with antidepressant response and TESI [94,95]. These studies may be particularly helpful when conducted prospectively in treatment samples, as they can provide information on gene-expression changes before and after treatment, which may be etiologically relevant. As these studies are limited to investigation of gene expression in peripheral samples, at best, they can only provide an estimate of CNS processes, but direct investigation of brain processes can be accomplished through the use of animal models of depression and antidepressant response [92,93,96].

While it is always preferable to use genome-wide strategies when the exact pathophysiological mechanisms involved in the phenotype being investigated are not

known, the single study included in this article that employed a genome-wide approach [21] used a low-density array with 100,000 SNPs. Similarly, with one notable exception [22], the studies reviewed here used relatively low-density marker panels when investigating candidate genes. Recent technological advances made available dense genotyping platforms to screen the entire genome ($\leq 1,000,000$ SNPs) as well as examine other types of genetic variations, such as copy number variants and deep sequencing. As deep sequencing methodologies become more feasible and accessible, future studies will no longer rely on genetic markers and, thus, will be significantly more powerful in capturing genetic variability, as has been illustrated by recent studies of treatment response in ethnic minorities [97].

Another limitation of the studies reviewed here was the almost exclusive focus on single-point analyses, although some did report haplotype analyses [13,14,22]. Based on gene-expression studies, it is more likely that a network of interacting genes is explanatory both of the pathophysiology of suicidal behavior and with respect to antidepressant treatment response. While some attempts have been made to examine gene–gene interactions and additive effects [14,18,21], owing to low power, most studies have focused on single gene effects or haplotype analyses within a single gene.

Statistical approaches—Common to all pharmacogenomic studies and specifically for those included in this article, a major limitation to being able to detect an association between a genetic marker and suicidal outcome is the relatively small sample size, as well as the lack of replications. While STAR*D is the largest treatment trial for major depressive disorder conducted so far and is well powered to investigate response to treatment, it is limited in the number of cases compared with controls [18,21]. Although the GENDEP study is smaller than STAR*D, it has a larger number of cases, owing to a different definition of the phenotype [14]. The TORDIA study is the first pharmacogenetic study in treatment-resistant depressed adolescents and has a very limited sample size [23]. Some studies analyzed their data stratifying for sex, age and drug, and tried to examine gene–drug interactions [13,14], thus increasing the number of multiple comparisons. These procedures further reduced power and increased the risk of Type I and II errors.

Many of these studies examined the specificity of their genetic findings to their phenotype of interest by controlling for confounders or other related phenotypes, such as past suicidal behavior and/or treatment response, using regression-based approaches [13,14,18,21]. This approach is only valid under the assumption that these confounders are not associated with the genetic marker, which was not the case in some of these studies [14]. In addition, it has been recently demonstrated that association tests with adjustment procedures based on regression approaches are biased, and may provide incorrect results [98].

All the studies took into account the issue of population stratification using different approaches: restricting the analysis to subjects of European ancestry, controlling for race, checking for population stratification using a clustering method based on a modest number of SNPs or using genomic control. These are appropriate techniques given the limited samples available for analysis. New statistical methods are now available to provide more efficient ways to correct for population stratification and the selection of controls in GWAS based on spectral graph theory, SpectralGEM [99]. The future use of these novel approaches in pharmacogenomic studies will depend on the availability of large samples.

Future perspective

In future pharmacogenomics studies, the definition of the suicidal phenotype should describe a phenomenon that is clinically significant, that is, a change in suicidal ideation or

behavior that warrants a change in treatment. Suicidal outcomes should be reported alongside response, medication side effects and measures of adherence and drug concentration in order to generate genetic profiles that simultaneously examine risk and benefit. Current life stressors and early childhood adversity should be assessed because these may affect treatment response or suicidal outcome and may interact with risk markers.

The recommended strategy for future genetic studies is to examine different genetic variations using available technologies of dense-marker genome-wide SNP arrays, copy number variations and dense sequencing of areas of interest, coupled with gene expression and proteomic studies, to generate putative pathways and networks of genes implicated in suicidal phenotypes. Measures of cognitive and biological biomarkers of treatment response and suicidal ideation and behavior should also be incorporated into genetic studies. Such approaches may help research to go beyond association to explicate biological mechanisms whereby antidepressants are associated with an increased risk for suicidal events.

Future studies should incorporate a sample of sufficient size that covers a wide enough age range to be able to detect age- and sex-specific effects, since risk for treatment-emergent suicidal events varies substantially by age and sex.

Pharmacogenomic approaches hold promise for being able to identify those individuals who are at greatest risk for experiencing a suicidal event. Furthermore, the identification of genetic markers associated with increased risk for suicidal events may give clues as to the etiology of these events, as well as possible therapeutic targets.

Executive summary

Findings

- A total of six studies examining the pharmacogenomics of suicidal events in antidepressant-treated depressed patients were reviewed.
- Nearly all (97%) of the reported suicidal events were increases in ideation rather than suicidal behavior.
- Associations were reported for genes involved in neuroprotection, transcription, glutamatergic and noradrenergic neurotransmission, inflammatory and stress response, and synthesis of glycoproteins.
- Replication of the associations of glutamatergic genes with the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study sample and broadly within a European sample were reported.
- Findings persisted after adjustment for past suicidal behavior, current ideation, depressive severity and clinical response.

The suicidal phenotype & its clinical significance

- The definition of phenotype was not consistent across studies, although one study demonstrated that its findings were robust to variation in definition.
- The definitions encompassed a wide range of suicidal behavior, from passive ideation to actual behavior, including ideation of low clinical significance that would not necessarily result in any change in treatment plan.
- No pharmacogenomic studies simultaneously examining the inter-relationship between genes and antidepressant exposure, response, side effects and suicidal events have been carried out.

Relationship to treatment

- Although none of the studies were placebo controlled, the events are likely to be due to treatment because they occurred early, risk markers were associated with earlier time to onset of an event, and because of some evidence of treatment-specificity, that is, polymorphisms in noradrenergic receptor associated with events only in those treated with a noradrenergic agent (nortryptiline).

Genetics & neurobiology of suicidal events

- Studies mostly examined candidate genes, with only one low-density genome scan conducted in a small sample. However, in the absence of a model for the etiology of increases in suicidal events in antidepressant treatment, it is difficult to ascertain biological plausibility, although most of the implicated genes are related to systems associated with the risk for depression or for suicidal behavior, which may undercut the argument that they are treatment specific.

Moderation by age & sex

- The US FDA reports show that there is an increase in suicidal events in antidepressants versus placebo only in those under the age of 25 years.
- Most of these pharmacogenomic samples did not include adolescents, and consequently, none were powered to test moderation by age, despite evidence that suicidal events in antidepressant treatment are likely to be different in younger versus older samples.
- Two sex-specific findings were reported, conveying higher risk in males (*CREB1* and *ADRA2A*).

Bibliography

Papers of special note have been highlighted as:

▪ of interest

1. Teicher MH, Glod CA, Cole JO. Antidepressant drugs and the emergence of suicidal tendencies. *Drug Safety* 1993;8:186–212. [PubMed: 8452661]
2. Healy D, Whitaker C. Antidepressants and suicide: risk–benefit conundrums. *J Psychiatry Neurosci* 2003;28:331–337. [PubMed: 14517576]
3. Olfson M, Marcus SC, Shaffer D. Antidepressant drug therapy and suicide in severely depressed children and adults: a case–control study. *Arch Gen Psychiatry* 2006;63:865–872. [PubMed: 16894062]
4. Stone M, Laughren T, Jones ML, 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;11:339–342.
5. Gibbons RD, Brown CH, Hur K, et al. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *Am J Psychiatry* 2007;164:1356–1363. [PubMed: 17728420]
6. Gibbons R, Brown CH, Hur K, Marcus S, Bhaumik DK, Mann JJ. The relationship between antidepressants and suicide: results of analysis of the Veterans Health Administration datasets. *Am J Psychiatry* 2007;164:1044–1049. [PubMed: 17606656]
7. Olfson M, Shaffer D, Marcus SC, Greenberg T. Relationship between antidepressant medication treatment and suicide in adolescents. *Arch Gen Psychiatry* 2003;60:978–982. [PubMed: 14557142]
8. Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant medication use and rate of suicide. *Arch Gen Psychiatry* 2005;62:165–172. [PubMed: 15699293]

9. Ludwig J, Marcotte DE, Norberg K. Anti-depressants and suicide. *J Health Economics* 2009;28:659–676.
10. Posner K, Oquendo M, Stanley B, Davies M, Gould M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry* 2007;164:1035–1043. [PubMed: 17606655]
11. Libby AM, Orton HD, Valuck RJ. Persisting decline in depression treatment after FDA warnings. *Arch Gen Psychiatry* 2009;66:633–639. [PubMed: 19487628]
12. Zisook S, Trivedi MH, Warden D, et al. Clinical correlates of the worsening or emergence of suicidal ideation during SSRI treatment of depression: an examination of citalopram in the STAR*D study. *J Affect Disord* 2009;117:63–73. [PubMed: 19217668]
13. Perlis RH, Purcell S, Fava M, et al. Association between treatment-emergent suicidal ideation with citalopram and polymorphisms near cyclic adenosine monophosphate response element binding protein in the STAR*D study. *Arch Gen Psychiatry* 2007;64:689–697. [PubMed: 17548750]
14. Perroud N, Aitchison KJ, Uher R, et al. Genetic predictors of increase in suicidal ideation during antidepressant treatment in the GENDEP project. *Neuropsychopharmacology* 2009;34:2517–2528. [PubMed: 19641488]
15. Brent DA, Emslie G, Clarke G, et al. Predictors of spontaneous and systematically assessed suicidal adverse events in the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) Study. *Am J Psychiatry* 2009;166:418–426. [PubMed: 19223438]
16. Vitiello B, Silva SG, Rohde P, et al. Suicidal events in the Treatment of Adolescents with Depression Study (TADS). *J Clin Psychiatry* 2009;70:741–747. [PubMed: 19552869]
17. Perlis RH, Beasley CM Jr, Wines JD Jr, et al. Treatment-associated suicidal ideation and adverse effects in an open, multicenter trial of fluoxetine for major depressive episodes. *Psychother Psychosom* 2007;76:40–46. [PubMed: 17170562]
18. Laje G, Paddock S, Manji H, et al. Genetic markers of suicidal ideation emerging during citalopram treatment of major depression. *Am J Psychiatry* 2007;164:1530–1538. [PubMed: 17898344]
19. Seemuller F, Riedel M, Obermeier M, et al. The controversial link between antidepressants and suicidality risks in adults: data from a naturalistic study on a large sample of in-patients with a major depressive episode. *Int J Neuropsychopharmacol* 2009;12:181–189. [PubMed: 18662490]
20. Laje G, Perlis RH, Rush AJ, McMahon FJ. Pharmacogenetics studies in STAR*D: strengths, limitations, and results. *Psychiatr Serv* 2009;60:1446–1457. [PubMed: 19880459]
21. Laje G, Allen AS, Akula N, Manji H, John Rush A, McMahon FJ. Genome-wide association study of suicidal ideation emerging during citalopram treatment of depressed outpatients. *Pharmacogenet Genomics* 2009;19:666–674. [PubMed: 19724244]
22. Menke A, Lucae S, Kloiber S, et al. Genetic markers within glutamate receptors associated with antidepressant treatment-emergent suicidal ideation. *Am J Psychiatry* 2008;165:917–918. [PubMed: 18593792]
23. Brent DA, Melhem N, Ferrell R, et al. Association of *FKBP5* polymorphisms with suicidal events in the Treatment of Resistant Depression in Adolescents (TORDIA) study. *Am J Psychiatry* 2010;167(2):190–197. [PubMed: 20008943]
24. Perlis RH, Purcell S, Fagerness J, et al. Clinical and genetic dissection of anger expression and *CREB1* polymorphisms in major depressive disorder. *Biol Psychiatry* 2007;62:536–540. [PubMed: 17300755]
25. Dwivedi Y, Rao JS, Rizavi HS, et al. Abnormal expression and functional characteristics of cyclic adenosine monophosphate response element binding protein in postmortem brain of suicide subjects. *Arch Gen Psychiatry* 2003;60:273–282. [PubMed: 12622660]
26. Odagaki Y, Garcia-Sevilla JA, Huguelet P, La Harpe R, Koyama T, Guimon J. Cyclic AMP-mediated signaling components are upregulated in the prefrontal cortex of depressed suicide victims. *Brain Res* 2001;898:224–231. [PubMed: 11306008]
27. Young LG, Bezchlibnyk YB, Chen B, Wang JF, MacQueen GM. Amygdala cyclic adenosine monophosphate response element binding protein phosphorylation in patients with mood disorders: effects of diagnosis, suicide and drug treatment. *Biol Psychiatry* 2004;55:570–577. [PubMed: 15013825]

28. Rush AJ, Bernstein IH, Trivedi MH, et al. An evaluation of the quick inventory of depressive symptomatology and the Hamilton rating scale for depression: a sequenced treatment alternatives to relieve depression trial report. *Biol Psychiatry* 2006;59:493–501. [PubMed: 16199008]
29. Carlson CS, Eberle MA, Rieder MJ, Yi Q, Kruglyak L, Nickerson DA. Selecting a maximally informative set of single-nucleotide polymorphisms for association analyses using linkage disequilibrium. *Am J Hum Genet* 2004;74(1):106–120. [PubMed: 14681826]
30. Hambleton, RK.; Swaminathan, H.; Rogert, HJ. *Fundamentals of Item Response Theory*. Sage Press; CA, USA: 1991.
31. Perroud N, Uher R, Marusic A, et al. Suicidal ideation during treatment of depression with escitalopram and nortriptyline in genome-based therapeutic drugs for depression (GENDEP): a clinical trial. *BMC Med* 2009;7:60. [PubMed: 19832967]
32. Bridge J, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *J Am Med Assoc* 2007;297:1683–1696.
33. Bridge J, Barbe RP, Birmaher B, Kolko DJ, Brent DA. Emergent suicidality in a clinical psychotherapy trial for adolescent depression. *Am J Psychiatry* 2005;162:2173–2175. [PubMed: 16263860]
34. Mann JJ, Waternaux C, Haas GL, Malone KM. Toward a clinical model of suicidal behavior in psychiatric patients. *Am J Psychiatry* 1999;156(2):181–189. [PubMed: 9989552]
35. Brent DA, Mann JJ. Family genetic studies, suicide, and suicidal behavior. *Am J Med Genet* 2005;133C:13–24. [PubMed: 15648081]
36. Mann JJ. Neurobiology of suicidal behavior. *Nat Rev Neurosci* 2003;4:819–828. [PubMed: 14523381]
37. Brent DA, Oquendo MA, Birmaher B, et al. Peripubertal suicide attempts in offspring of suicide attempters with siblings concordant for suicidal behavior. *Am J Psychiatry* 2003;160(8):1486–1493. [PubMed: 12900312]
38. McGirr AM, Alda M, Seguis M, Cabot S, Lesage A, Turecki G. Familial aggregation of suicide is explained by cluster B traits: a three-group family study of suicide controlling for major depressive disorder. *Am J Psychiatry* 2009;166:1124–1134. [PubMed: 19755577]
39. Melhem NM, Brent DA, Ziegler M, et al. Familial pathways to early-onset suicidal behavior: familial and individual antecedents of suicidal behavior. *Am J Psychiatry* 2007;164:1364–1370. [PubMed: 17728421]
40. Meltzer HY, Alphas L, Green AI, et al. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry* 2003;60:82–91. [PubMed: 12511175]
41. Akiskal H, Benazzi F. Does the FDA proposed list of possible correlates of suicidality associated with antidepressants apply to an adult private practice population? *J Affect Disord* 2006;94:105–110. [PubMed: 16766043]
42. Hansen L, Kingdom D. Akathisia as a risk factor for suicide. *Br J Psychiatry* 2006;188:192–195. [PubMed: 16449715]
43. Smith EG. Association between antidepressant half-life and the risk of suicidal ideation or behavior among children and adolescents: confirmatory analysis and research implications. *J Affect Disord* 2009;114:143–148. [PubMed: 18692250]
44. Lotrich FE, Pollock BG, Kirshner M, Ferrell RF, Reynolds CF 3rd. Serotonin transporter genotype interacts with paroxetine plasma levels to influence depression treatment response in geriatric patients. *J Psychiatry Neurosci* 2008;33:123–130. Demonstrates the importance of assessing drug concentration in pharmacogenomic studies. [PubMed: 18330458]
45. Lotrich FE, Bies RR, Smith GS, Pollock BG. Relevance of assessing drug concentration exposure in pharmacogenetic and imaging studies. *J Psychopharmacol* 2006;20(4 Suppl):33–40. [PubMed: 16785268]
46. Zackrisson AL, Lindblom B, Ahlner J. High frequency of occurrence of *CYP2D6* gene duplication/multiduplication indicating ultrarapid metabolism among suicide cases. *Clin Pharmacol Ther*. 2009 (Epub ahead of print). Demonstrates an association between

- polymorphisms in the *CYP2D6* gene, which leads to ultrafast metabolisms of certain antidepressants, and suicide. 10.1038/clpt.2009.216
47. Kawanishi C, Lundgren S, Agren H, Bertilsson L. Increased incidence of *CYP2D6* gene duplication in patients with persistent mood disorders: ultrarapid metabolism of antidepressants as a cause of nonresponse. A pilot study. *Eur J Clin Pharmacol* 2004;59:803–807. [PubMed: 14652703]
 48. Brent DA. In search of endophenotypes for suicidal behavior. *Am J Psychiatry* 2009;166:1087–1089. [PubMed: 19797437]
 49. Mann JJ, Arrango VA, Avenevoli S, et al. Candidate endophenotypes for genetic studies of suicidal behavior. *Biol Psychiatry* 2009;65:556–563. Excellent overview of relevant possible endophenotypes for suicidal behavior that might be examined in future pharmacogenomic studies. [PubMed: 19201395]
 50. Dowlatshahi D, MacQueen GM, Wang JF, Young LT. Increased temporal cortex CREB concentrations and antidepressant treatment in major depression. *Lancet* 1998;352:1754–1755. [PubMed: 9848357]
 51. Tsai S-J. Possible involvement of the BDNF-dependent pathway in treatment-emergent suicidality or decreased response to antidepressants. *Med Hypotheses* 2005;65:942–946. [PubMed: 16002234]
 52. Dwivedi Y. Brain-derived neurotrophic factor: role in depression and suicide. *Neuropsychiatr Disord Treat* 2009;5:433–449. Comprehensive review of the role of BDNF in suicide and depression.
 53. Sarchiapone M, Carli V, Roy A, et al. Association of polymorphism (Val66Met) of brain-derived neurotrophic factor with suicide attempts in depressed patients. *Neuropsychobiology* 2008;57:139–145. [PubMed: 18600033]
 54. Kim B, Kim CY, Hong JP, Lee C, Joo YH. Brain-derived neurotrophic factor Val/Met polymorphism and bipolar disorder. Association of the Met allele with suicidal behavior of bipolar patients. *Neuropsychobiology* 2008;58:97–103. [PubMed: 18843195]
 55. Wagner S, Baskaya O, Dahmen N, Lieb K, Tadic A. Modulatory role of the brain-derived neurotrophic factor ValMet polymorphism on the effects of serious life events on impulsive aggression in borderline personality disorder. *Genes Brain Behav* 2010;9:97–102. [PubMed: 19817874]
 56. Henningsson S, Borg J, Lundberg J, et al. Genetic variation in brain-derived neurotrophic factor is associated with serotonin transporter but not serotonin-1A receptor availability in men. *Biol Psychiatry* 2009;66:477–485. [PubMed: 19500776]
 57. Ernst C, Mechawar N, Turecki G. Suicide neurobiology. *Progr Neurobiol* 2009;89:315–333. Comprehensive review of the neurobiology of suicide.
 58. Kohli MA, Salyakina D, Pfennig A, et al. Association of genetic variants in the neurotrophic receptor-encoding gene *NTRK2* and a lifetime history of suicide attempts in depressed patients. *Arch Gen Psychiatry* 2010;67:E1–E12.
 59. Pandey GN, Dwivedi Y. Noradrenergic function in suicide. *Arch Suicide Res* 2007;11:235–246. [PubMed: 17558608]
 60. Sequeira A, Mamdani F, Lalovic A, et al. α 2A adrenergic receptor gene and suicide. *Psychiatry Res* 2004;125:87–93. [PubMed: 15006432]
 61. Palucha A, Pilc A. The involvement of glutamate in the pathophysiology of depression. *Drug News Perspect* 2005;18:262–268. [PubMed: 16034483]
 62. Martinez-Turrillas R, Frechilla D, Del Río J. Chronic antidepressant treatment increases the membrane expression of AMPA receptors in rat hippocampus. *Neuropharmacology* 2002;43(8):1230–1237. [PubMed: 12527472]
 63. Barbon A, Popoli M, La Via L, et al. Regulation of editing and expression of glutamate α -aminopropionic acid (AMPA)/kainate receptors by antidepressant drugs. *Biol Psychiatry* 2006;59:713–720. [PubMed: 16460696]
 64. Price RB, Nock MK, Charney DS, Mathew SJ. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biol Psychiatry* 2009;66:522–526. [PubMed: 19545857]

65. Sequeira A, Mamdani F, Ernst C, et al. Global brain gene expression analysis links glutamatergic and GABAergic alterations to suicide and major depression. *PLoS One* 2009;4:E6585. [PubMed: 19668376]
66. Pace TW, Miller AH. Cytokines and glucocorticoid receptor signaling. *Ann NY Acad Sci* 2009;1179:86–105. [PubMed: 19906234]
67. Anisman H, Merali Z. Cytokines, stress and depressive illness: brain-immune interactions. *Ann Med* 2003;35:2–11. [PubMed: 12693607]
68. Lindqvist D, Janelidze S, Hagell P, et al. Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. *Biol Psychiatry* 2009;66:287–292. [PubMed: 19268915]
69. Saiz PA, Garcia-Portilla P, Paredes B, et al. Association study of the interleukin-1 gene complex and tumor necrosis factor α gene with suicide attempts. *Psychiatric Genet* 2008;18:147–150.
70. Omrani MD, Bushehri B, Bagheri M, Salari-Lak S, Alipour A, Anoshae MR, et al. Role of *IL-10-1-82*, *IFN- γ +874*, and *TNF- α -308* genes polymorphisms in suicidal behavior. *Arch Suicide Res* 2009;13:330–339. [PubMed: 19813110]
71. Ising M, Depping A-M, Siebertz A, et al. Polymorphisms in the *FKBP5* gene region modulate recovery from psychosocial stress in healthy controls. *Eur J Neuroscience* 2008;28:389–398.
72. Scammell JG, Hubler TR, Denny WB, Valentine DL. Organization of the human FK506-binding immunophilin *FKBP52* protein gene (*FKBP4*). *Genomics* 2003;81:640–643. [PubMed: 12782134]
73. Denny WB, Valentine DL, Reynolds PD, Smith DF, Scammell JG. Squirrel monkey immunophilin *FKBP51* is a potent inhibitor of glucocorticoid receptor binding. *Endocrinology* 2000;141:4107–4113. [PubMed: 11089542]
74. Mann JJ, Currier D. A review of prospective studies of biologic predictors of suicidal behavior in mood disorders. *Arch Suicide Res* 2007;11:3–16. [PubMed: 17178639]
75. Roy A, Gorodetsky E, Yuan Q, Goldman D, Enoch M-A. Interaction of *FKBP5*, a stress-related gene, with childhood trauma increases the risk for attempting suicide. *Neuropsychopharmacology*. 2010 (Epub ahead of print). 10.1038/npp.2009.236
76. Binder EB, Bradley RG, Liu W, et al. Association of *FKBP5* polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *J Am Med Assoc* 2008;19:1291–1305.
77. Binder EB. The role of *FKBP5*, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders. *Psychoneuroendocrinology* 2009;34:S186–S195. [PubMed: 19560279]
78. Zobel A, Schuhmacher A, Jessen F, Hofels S, von Widdern O, Metten M, et al. DNA sequence variants of the *FKBP5* gene are associated with unipolar depression. *Int J Neuropsychopharmacol* 2010;5:1–12. [PubMed: 20701824]
79. Currier D, Mann JJ. Stress, genes and the biology of suicidal behavior. *Psychiatr Clin North Am* 2008;31:247–269. [PubMed: 18439448]
80. Schosser A, Kasper S. The role of pharmacogenetics in the treatment of depression and anxiety disorders. *Int Clin Psychopharmacol* 2009;24:277–288. [PubMed: 19738481]
81. Joyce PR, Mulder RT, Luty SE, et al. Age-dependent antidepressant pharmacogenomics: polymorphisms of the serotonin transporter and G protein $\beta 3$ subunit as predictors of response to fluoxetine and nortriptyline. *Int J Neuropsychopharmacol* 2003;6:339–3466. [PubMed: 14604448]
82. Mulder RT, Watkins WGA, Joyce PR, Luty SE. Age may affect response to antidepressants with serotonergic and noradrenergic actions. *J Affect Disord* 2003;76:143–149. Reports that age mediates antidepressant response, supporting the testing of age moderation in pharmacogenomic studies. [PubMed: 12943944]
83. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the *5-HT* gene. *Science* 2003;301:386–389. [PubMed: 12869766]
84. Barbe RP, Bridge J, Birmaher B, Kolko DJ, Brent DA. Lifetime history of sexual abuse, clinical presentation, and outcome in a clinical trial for adolescent depression. *J Clin Psychiatry* 2004;65(1):77–83. [PubMed: 14744173]

85. Asarnow JR, Emslie G, Clarke G, et al. Treatment of selective serotonin reuptake inhibitor-resistant depression in adolescents: predictors and moderators of treatment response. *J Am Acad Child Adolesc Psychiatry* 2009;48:330–339.
86. Nemeroff CB, Heim CM, Thase ME, et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *Proc Natl Acad Sci USA* 2003;100(24):14293–14296. [PubMed: 14615578]
87. Kaufman J, Yang BZ, Douglas-Palumberi H, et al. Brain-derived neurotrophic factor-5-*HTTLPR* gene interactions and environmental modifiers of depression in children. *Biol Psychiatry* 2006;59(8):673–680. [PubMed: 16458264]
88. Roy A. Self-rated childhood emotional neglect and CSF monoamine indices in abstinent cocaine-abusing adults: possible implications for suicidal behavior. *Psychiatry Res* 2009;112:69–75. [PubMed: 12379452]
89. Brunner J, Bronisch T, Uhr M, et al. Proteomic analysis of the CSF in unmedicated patients with major depressive disorder reveals alterations in suicide attempters. *Eur Arch Psychiatr Clin Neurosci* 2005;255:438–440. Illustrates the potential of proteomics in the study of psychiatric genetics.
90. Romeo MJ, Espina V, Lowenthal M, Espina BH, Petricoin EF 3rd, Liotta LA. CSF proteome: a protein repository for potential biomarker identification. *Expert Rev Proteomics* 2005;2(1):57–70. [PubMed: 15966853]
91. Marais L, Hattingh SM, Stein DJ, Daniels WM. A proteomic analysis of the ventral hippocampus of rats subjected to maternal separation and escitalopram treatment. *Metab Brain Dis* 2009;24:569–586. [PubMed: 19838779]
92. Ernst C, Bureau A, Turecki G. Application of microarray outlier detection methodology to psychiatric research. *BMC Psychiatry* 2008;8:29. Review of the potential of gene expression studies using microarray technology to the study of psychiatric genetics. [PubMed: 18433482]
93. Sequeira A, Turecki G. Genome wide gene expression studies in mood disorder. *OMICS* 2006;10:444–454. [PubMed: 17233556]
94. McGowan PO, Sasaki A, Huang TC, et al. Promoter-wide hypermethylation of the ribosomal RNA gene promoter in the suicide brain. *PLoS One* 2008;3:E2085. [PubMed: 18461137]
95. Ernst C, Sequeira A, Klempan T, Ernst N, Ffrench-Mullen JM, Turecki G. Confirmation of region-specific patterns of gene expression in the human brain. *Neurogenetics* 2007;8:219–224. [PubMed: 17375343]
96. Leuchter AF, Cook IA, Hunter AM, Korb AS. A new paradigm for the prediction of antidepressant treatment response. *Dialogues Clin Neurosci* 2009;11:435–446. [PubMed: 20135901]
97. Licinio J, Dong C, Wong M-L. Novel sequence variations in the brain-derived neurotrophic factor gene and association with major depression and antidepressant treatment response. *Arch Gen Psychiatry* 2009;66:488–497. Demonstrates the potential contributions of deep sequencing in order to understand pharmacogenomic responses. [PubMed: 19414708]
98. Vansteelandt S, Goetgheuk S, Lutz S, et al. On the adjustment for covariates in genetic association analysis: a novel, simple principle to infer direct causal effects. *Genet Epidemiol* 2009;33:394–405. [PubMed: 19219893]
99. Lee AB, Luca D, Klei L, Devlin B, Roeder K. Discovering genetic ancestry using spectral graph theory. *Genet Epidemiol* 2010;34(1):51–59. [PubMed: 19455578]

Summary of pharmacogenetic studies of suicidal events in depression.

Table 1

Study (year)	Patients (n)	Sample/treatment	Phenotype/frequency	Genes studied	Gene associated with phenotype	rs	p-value	Covariates	Comments	Ref.
Perlis <i>et al.</i> (2007)	1447	STAR*D/citalopram	Baseline QIDS-C-12 of ≤1 and increase to ≥2 TESI (males): 54 out of 539 (10.0%) One attempt (0.18%)	<i>CREBI</i> 44 SNPs	<i>CREBI</i>	7569963G 4675690T	0.005 0.005	Severity of depression; use of hypnotic; history of attempt	Findings significant in males only; p-value not corrected for stratification by sex; covariates tested one at a time; markers also predict earlier time to event	[13]
Laje <i>et al.</i> (2007)	1862	STAR*D/citalopram	Baseline QIDS-S-12 = 0; increase to ≥1 TESI: 120/1862 (6.4%); One attempt (0.05%) Controls: QIDS-S-12 = 0 during treatment	68 genes; 768 SNPs	<i>GRIK2</i> <i>GRIA3</i>	2518224 CC 4825476G	<0.003 <0.01	Remission; increase in citalopram dose	Findings robust to variation in phenotype definition; 69% of events occurred by third week; not related to current ideation or previous attempt	[18]
Laje <i>et al.</i> (2009)	274 (90 cases)	STAR*D/citalopram	Same as [18] recurrent depression; no hx ideation or attempt	Genome-wide association 109,365 SNPs	<i>PAPLN</i> <i>IL28RA</i>	11628713C 10903034AA	0.01 0.06	Same as [18]	Replicated findings in entire STAR*D sample	[21]
Perroud <i>et al.</i> (2009)	796	GENDEP/nortriptyline or escitalopram	Combination of MADRS-10, HAM-D-3 and BDI-9; require 0.5 SD increase; controls = no change TESI/TWOSI: 254 out of 796 (31.9%) Two attempts, one completion (0.38%)	Nine genes, 127 SNPs, Two VNTRs	<i>BDNF</i> <i>NTRK2</i> haplotype <i>BDNF</i> × <i>NTRK2</i> <i>ADRA2A</i> × drug	962369G GGTT GGTC 11195419A	0.04 0.046 0.014 0.01 <0.0016	Suicide attempt; response; baseline depression severity	<i>BDNF</i> , <i>NTRK2</i> haplotypes, <i>BDNF</i> × <i>NTRK2</i> associated in either escitalopram or nortriptyline; <i>ADRA2A</i> only in those on nortriptyline and in males	[14]
Menke <i>et al.</i> (2008)	397	MARS/physician choice (wide range of antidepressants)	HAM-D-3 increase from 0; controls, 0 or same throughout (results here are for controls = 0) TESI: 32 out of 397 (8.1%) No attempts reported Three completions (0.08%)	<i>GRIK2</i> 112 SNPs <i>GRIA3</i> 17 SNPs	<i>GRIK2</i> <i>GRIA3</i>	2518224 2852618A 954765A 2782900T 4825476A	0.86 0.005 0.007 0.007 0.04		Although results broadly parallel those of [18], different <i>GRIK2</i> risk allele associated with ideation	[22]
Brent <i>et al.</i> (2010)	176	TORDIA/paroxetine, citalopram, fluoxetine, venlafaxine	Spontaneous report or B-SSRS increase of ≥1 Controls: no change TESI: 18 out of 176 (10.2%) Four attempts (2.2%)	12 genes; 21 SNPs	<i>FKBP5</i>	1360780T 3800373G	0.025 0.025	CBT; medication; CBT × medication; CBQ-A; CBQ-A × genotype; trazodone use	All participants were aged 12–18 years; homozygous genotypes were associated with decreased time to event	[23]

BDI: Beck Depression Inventory; B-SSRS: Brief Suicide Severity Rating Scale; CBT: Cognitive behavioral therapy; GENDEP: European Genome-based Therapeutic Drugs for Depression Study; HAM-D: Hamilton Depression Rating Scale; hx: History; MADRS: Montgomery–Asberg Depression Rating Scale; MARS: Munich Antidepressant Response Signature Study; QIDS-C: Quick Inventory of Depressive Symptoms (Clinician Version); QIDS-S: Quick Inventory of Depressive Symptoms (Self-Report); SD: Standard deviation; STAR*D: Sequenced Treatment Alternatives to Relieve Depression Study; TESI: Treatment-emergent suicidal ideation; TORDIA: Treatment of SSRI-Resistant Depression in Adolescents Study; TWOSI: Treatment-worsening suicidal ideation.