J Neural Transm (2016) 123:1347–1354
DOI 10.1007/s00702-016-1585-7

PSYCHIATRY AND PRECLINICAL PSYCHIATRIC STUDIES - ORIGINAL ARTICLE

Pharmacogenetics of citalopram-related side effects in children with depression and/or anxiety disorders

Maya Amitai[1,2,3] · Sefi Kronenberg[4] · Miri Carmel[2,5] · Elena Michaelovsky[2,5] · Amos Frisch[2,5] · David Brent[6,7] · Alan Apter[1,2] · Alon Chen[3,9] · Abraham Weizman[2,5,8] · Silvana Fennig[1,2]

Received: 25 March 2016 / Accepted: 12 June 2016 / Published online: 20 June 2016

Abstract Pharmacogenetic approach to antidepressant (AD) response is a promising avenue toward individualizing AD treatment. This is particularly relevant in pediatric populations because of concerns about the suicide risk of serotonin selective reuptake inhibitors (SSRIs), resulting in a black-box warning. However, to date, no specific gene or polymorphism has been consistently implicated as a marker of AD side effect (SE) in the pediatric population. The aim of this study was to examine the association between polymorphisms in genes related to the serotonergic system and citalopram SE's in children and adolescents with major depressive disorder (MDD)/dysthymia and/or anxiety disorders. Outpatients ($N = 87$, 44 % males), aged 7–18 years with a DSM-IV-TR diagnosis of MDD/dysthymia and/or an anxiety disorder were treated in an 8-week open trial with 20–40 mg/day of citalopram. SE's were rated using a questionnaire devised specifically for this study. Association analysis between known/candidate genetic variants in three genes (5-HTR2A, 5-HTR1Dβ, 5-HTR2C) and SE's was conducted. Agitation was more common in boys than girls (male:female 42.1 vs. 18.7 %, $\chi^2 = 5.61$, $df = 1$, $p = 0.018$). Subjects with 5-HTR1Dβ CC genotype showed more agitation vs. both CG and GG genotypes (CC:CG:GG 71.4 vs. 33.3 vs. 18.1 %, $\chi^2 = 8.99$, $df = 2$, $p = 0.011$). The 5-HTR1Dβ CC genotype was associated with more reports of agitation. It has been suggested that agitation may be an intermediate phenotype to suicidal behavior. Thus, it seems that 5-HTR1Dβ polymorphism may be involved in citalopram-related agitation in children and adolescents treated for depression and/or anxiety.

Keywords Children and adolescents · Citalopram · Depression · Anxiety · Pharmacogenetics

Introduction

While antidepressants (ADs) are widely prescribed for depression and anxiety disorders in children and adolescents, clinical trials suggest that only 50–60 % of patients

M. Amitai and S. Kronenberg equally contributed to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s00702-016-1585-7) contains supplementary material, which is available to authorized users.

✉ Maya Amitai
maya.amitai@weizmann.ac.il

[1] Department of Psychological Medicine, Schneider Children's Medical Center of Israel, Petach Tikva, Israel

[2] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[3] The Ruhman Family Laboratory for Research on the Neurobiology of Stress, Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel

[4] Department of Psychiatry, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

[5] Felsenstein Medical Research Center, Petach Tikva, Israel

[6] Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

[7] Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

[8] Research Unit, Geha Mental Health Center, Petach Tikva, Israel

[9] Department of Stress Neurobiology and Neurogenetics, Max-Planck Institute of Psychiatry, Munich, Germany

respond to any single AD (Papakostas 2009), and clinical experience suggests even lower response rates (Kirchheiner et al. 2004; Souery et al. 2007). In addition to the difficulty in identifying an efficient treatment, AD use is frequently associated with intolerable adverse drug reactions. Inability to tolerate side-effects (SEs) is the reason for discontinuing AD therapy in 30 % of adults treated with tricyclic ADs or SSRIs (Maddox et al. 1994). A high risk of discontinuation due to SE was noted in a recent meta-analysis in young patients treated with tricyclic ADs as compared to those treated with SSRIs (Qin et al. 2014). A recent meta-analysis assessing the efficacy and tolerability of ADs in pediatric anxiety disorders found no indication of increased risk of discontinuation treatment due to side effects (Strawn et al. 2015), however, a trend towards activation symptoms was reported. Clinicians currently have no way to predict individual efficacy and SE profiles, and a trial-and-error switching paradigm often leaves these patients in psychological distress for weeks and even months. The longer depression/anxiety persists, the greater the risk of developing chronic depression, suicidal ideation, and suicidal behavior. Clearly, improved methods of patient—AD matching to minimize SEs would greatly improve treatment outcome and tolerability.

Serious adverse events (SAE) following selective serotonin reuptake inhibitors (SSRIs) treatment, including suicidality, aggression, hyperarousal, agitation and antidepressant-induced mania (AIM) have been extensively reported (Strawn et al. 2014; Cheung et al. 2005; Amitai et al. 2015; Adegbite-Adeniyi et al. 2012; Gibbons et al. 2012). A meta-analysis of adverse event reports (AERs) of suicidal thoughts and behaviors from 25 randomized controlled trials revealed an overall odds ratio (OR) of 1.78 (95 % CI 1.14–2.77), indicating that the rate of suicidal thoughts and behaviors was significantly higher in children randomized to active AD treatment relative to placebo (Bridge et al. 2007; Hammad et al. 2006).

Pharmacogenetic approach to predict AD response is a promising avenue toward individualizing AD treatment (Lohoff and Ferraro 2010; Clark et al. 2012). However, to date there is no robust and consistent evidence implicating any specific candidate gene or polymorphism that is associated with AD response or side effect (SE) profile in pediatric population (Blazquez et al. 2012; Murphy et al. 2003). Preliminary pharmacogenetic research has suggested an important role for genes related to serotonin function in AD SEs (Kato and Serretti 2010; Murphy et al. 2003; Serretti and Artioli 2004). The serotonergic system is involved in the regulation of a variety of physiological functions relevant to the therapy of depression and anxiety.

In this study, we used a pharmacogenetic approach to search for genetic variations that may affect the susceptibility for citalopram-related SEs [to note, we reported on suicidal adverse events and pharmacogenetics elsewhere (Kronenberg et al. 2007)]. Here we test the hypothesis that genetic variants in serotonin (5-HT)-related candidate genes may confer a protective or a risk effect on citalopram-related adverse events [to note: genetic variants in two serotonin-related genes, serotonin transporter (5-HTTLPR) and tryptophan hydroxylase 2 (TPH2), were described previously by our group (Kronenberg et al. 2007; Rotberg et al. 2013)]. The present study focuses on the association between candidate gene variants of three serotonergic genes (5-HTR2A, 5-HTR1Dβ, 5-HTR2C) and the emergence of adverse events during citalopram treatment. Such a relevant and clinically important analysis was not performed in our two previous studies (Kronenberg et al. 2007; Rotberg et al. 2013).

Methods

Subjects

The data presented herein were collected as part of an 8-week, open-label effectiveness trial that has been described elsewhere (Kronenberg et al. 2007; Schirman et al. 2010). Our eligibility criteria included: age between 7 and 18 years, Israeli Jewish descent and a diagnosis of major depression/dysthymia or anxiety disorder according to the diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) criteria. The diagnosis had to be of at least moderate severity with a clinical global impressions-severity (GCI-S) score of ≥4, a level consistent with accepted guidelines for the use of ADs in children and adolescents (Bernstein and Shaw 1997; Birmaher et al. 1998). Exclusionary criteria included intellectual disability, organic brain syndrome, autistic spectrum disorders, history of hypomania or mania, psychosis, eating-disorders, attention deficit hyperactivity disorder (ADHD) and substance abuse. We focused on treatment-naïve pediatric population in an attempt to recruit a homogeneous sample with regard to previous exposure to ADs. In addition no co-medication was permitted throughout the study period (8 weeks). Patients, who were receiving psychotherapy at the time of study recruitment, were also excluded to evaluate the sole impact of medication.

Evaluation

Subjects were assessed at intake, 2, 4, 6, and 8 weeks. Diagnostic evaluation was conducted using the Hebrew version of the schedule for affective disorders and schizophrenia for school age children–present and lifetime version (K-SADS-PL) (Kaufman et al. 1997; Shanee et al.

1997). Overall clinical severity and improvement were assessed using the CGI-S and improvement (CGI-I) subscales, respectively (Guy 1976). Continuous measures of depression and anxiety were obtained using the children's depression rating scale-revised (CDRS-R) (Poznanski et al. 1985) and the screen for child anxiety related emotional disorders (SCARED) (Birmaher et al. 1997, 1999). To note, diagnostic tools have been described in detail elsewhere (Kronenberg et al. 2007). In addition, SEs were rated by the clinician using the SSRI Side effect Profile Inventory (SEPI), a questionnaire devised specifically for this study to detect the possible SEs and their severity. SEPI comprises of the 24 most common SEs known for SSRIs and was described previously (Kronenberg et al. 2007). The list of side effects was developed from those reported in recent literature on the use of SSRIs in children (see Kronenberg et al. 2007). Each SE was rated on a 5-point scale from 0 (none) to 4 (very severe). For details see Table 1 in the supplementary data.

Procedure

The study was approved by the Schneider Children's Hospital Review Board and the Israeli Ministry of Health Committee of Studies in human genetics. Informed consent was obtained from all participants and their parents. After a confirmatory diagnostic assessment, all subjects received citalopram. All subjects visited a psychiatrist (SK) once a week. SEs were evaluated weekly by direct questioning. Starting dosage for all patients was citalopram 10 mg/day for 1 week, and then increased to 20 mg/day through week 4. If the degree of improvement was minimal (CGI-I < 3) then the dosage of citalopram was increased from 20 to 40 mg/day on week 5. Both patients and clinicians were blind to the genotype.

Genetic assays

Candidate gene selection

In this study, three genes (5-HTR2A, 5-HTR1Dβ, 5-HTR2C) considered important in various neurobiological pathways associated with serotonergic activity, were chosen. Before the first dose of citalopram, 9 mL of whole blood was collected and DNA was extracted using a commercial kit (Roche Diagnostics, Basel, Switzerland). Genotyping of the most studied T102C polymorphism in 5-HTR2A gene (rs6313) was carried out using a modified version of a method described by Warren et al. (1993). Genotyping of the 5-HTR1Dβ G861C polymorphism (rs6296) was detected and determined using a modified version of a method described by Lappalainen et al. (1995a). Genotyping of the 5-HTR2C G68C nonsynonymous (Ser23Cys) polymorphism (rs6318) was carried out using a modified version of a method described by Lappalainen et al. (1995b). Research indicates that the Ser 23 allele is constitutively more active than the Cys 23 allele, with allele-specific analysis of receptor function showing functional differences in the activity of the Ser 23 minor allele relative to the Cys 23 allele (Brummett et al. 2013).

Data analysis

We examined the relationship between genotype and SEs in all the children who agreed to participate in the study. For statistical analysis, a SE is considered to be: (1) any report of at least moderate severity, or (2) at least two reports of mild severity, or (3) any SE that was reported on the last follow-up before a patient prematurely withdrew from the study, regardless of the reason for withdrawal. The relationship between genotype and SEs was assessed using standard univariate tests (χ^2). All tests were two-tailed and the significance level was set at 0.05. Bonferroni correction was used in order to minimize possible false positive results. Also, in order for an association to be considered as putative, the heterozygote genotype had to indicate an intermediate level of association as compared to the two homozygote genotypes.

Results

Study population

In all, 107 subjects met the eligibility criteria, of whom 95 agreed to participate in the trial. Of these, 87 subjects were included in the final analysis. Eight subjects were not included due to protocol breach or dropout before the first follow-up was conducted. Ten subjects discontinued/dropped-out because of SEs and were included in the final analysis. No differences were found between the subjects who were excluded from the final analysis and the subjects that were included with respect to sex, age, diagnosis and severity of diagnosis at baseline.

Demographic and clinical characteristics of the study sample are presented in Table 1. The sample comprised 44 % males. Mean age of the sample was 14.07 ± 2.67 years. Twenty-nine children (33 %) were under the age of 13. With regard to ethnic background, the proportion of subjects with 2 or more Ashkenazi grandparents was 65 %. With respect to diagnosis, 36 (41 %) had anxiety alone, 30 (35 %) had depressive disorder and 21 (24 %) had comorbid depression and anxiety disorders. Out of the children with depression, 24 had MDD, 4 had dysthymia and 2 had double depression. Anxiety here refers to any

Table 1 Demographic and clinical characteristics of the study sample ($N = 87$)

Characteristic	*N* (%)
Gender males (%)	38 (44)
Age < 13 years (%)	29 (33)
Diagnosis (%)	
Depression	30 (35)
Depression with anxiety disorder	21 (24)
Anxiety alone	36 (41)
Final drug dose	
20 mg/day	40 (46 %)
40 mg/day	41 (47 %)

anxiety disorder (according to DSM-IV-TR): generalized anxiety disorder ($N = 24$), separation anxiety disorder ($N = 20$), social anxiety disorder ($N = 14$), panic disorder ($N = 5$), specific phobia ($N = 4$) and obsessive compulsive disorder ($N = 4$). Most of the children had more than one anxiety disorder. For forty children in the sample (47 %), the final drug dose was 40 mg/day.

SEs per gender, age, disorder type, drug dose

SEs were grouped into the following categories: neurologic SE, gastric SE, activation group SE, sleeping disorders and sexual SE. For the rates of the different SEs that were reported during the course of the treatment (see Table 2). Most of these side effects were reported in our previous publication (Kronenberg et al. 2007).

As stated in the population and demographics subsection, ten patients withdrew from the study because of SEs; four patients developed akathisia-like symptoms, i.e., severe psychological or motor agitation; three patients reported perceptual distortions or hallucinations; two patients developed hypomania; and one patient reported severe gastrointestinal discomfort and insomnia. However, most reports of SEs were mild to moderate and did not affect adherence to the drug.

Agitation was more common in boys (male:female 42.1 vs. 18.7 %, $\chi^2 = 5.61$, $df = 1$, $p = 0.018$, see Fig. 1). No correlation was found with age or final citalopram dose.

No other correlation was found between SE profile and gender, age, diagnosis or dose. No differences were found between the groups with concomitant MDD and anxiety disorders compared to those with a sole MDD or anxiety disorder regarding age, gender, final citalopram dose or SE profile (data not shown).

Table 2 The 24 side effect (SE) profile of the study population as detected by the SSRI Side effect Profile Inventory (SEPI)

Side effect	*N* (%)
Sleep disorders	49 (56)
Fatigue	27 (31)
Insomnia	13 (15)
Hypersomnia	9 (11)
Neurological SE	45 (52)
Headache	17 (20)
Sweating	10 (12)
Dry mouth	9 (11)
Tremor	5 (6)
Blurred vision	3 (4)
Perceptual disturbances	1 (1)
Gastrointestinal SE	46 (53)
Decreased appetite	16 (19)
Increased appetite	7 (8)
Gastric discomfort	14 (16)
Nausea	7 (8)
Diarrhea	2 (2)
Vomiting	0
Activation SE	34 (39)
Agitation	25 (29)
Elevated mood	8 (9)
Increased anxiety	1 (1)
Sexual SE	4 (5)
Decreased libido	3 (4)
Delayed orgasm	1 (1)
Decreased sexual function	0
Affective dullness	3 (4)
Galactorrhea	0

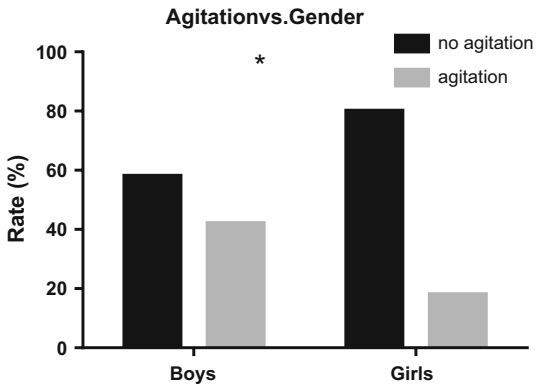

Fig. 1 The association between agitation and gender in the study sample. *$p < 0.05$—boys vs girls (agitation was significantly more common in boys)

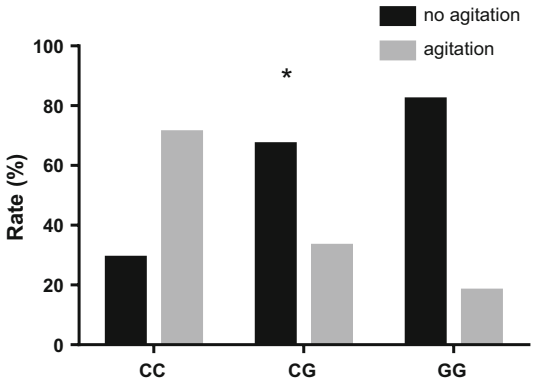

Fig. 2 The association between polymorphism of the 5-HTR1Dβ genotype (rs6296) and agitation. *$p < 0.05$ (remains significant after Bonferroni correction): Higher rates of agitation were detected in those with the 5-HTR1Dβ CC genotype compared to those with CG or GG

SEs by genotype

The distribution of the various SNPs assessed in the study sample is described in Table 2 in the Supplement data.

Higher rates of activation SE were observed in those with the 5-HTR1Dβ (rs6296) CC genotype compared to those with CG or GG (CC:CG:GG 71.4 vs. 39.3 vs. 22.7 %, $\chi^2 = 7.34$, $df = 2$, $p = 0.025$). Similarly, higher rates of agitation were detected in those with the 5-HTR1Dβ CC genotype compared to those with CG or GG (CC:CG:GG 71.4 vs. 33.3 vs. 18.1 %, $\chi^2 = 8.99$, $df = 2$, $p = 0.011$; see Fig. 2). This difference remained significant after Bonferroni correction for the three serotonergic genes.

All other differences between variations in genotype and SE were not significant following Bonferroni correction.

Discussion

SSRIs are among the most widely prescribed medications for the treatment of MDD and anxiety in youth, despite reports that they are associated with an increased incidence of a number of serious SEs, including suicidality, aggression, and violence, as well as AIM. Of particular, concern is the increased incidence of aggression observed in children and adolescents treated with SSRIs, since the temporal onset of these adverse effects often occurs within weeks of initiating SSRI treatment and may be related to SSRI induces suicidality (Amitai et al. 2015).

Behavioral activation was described in the majority of clinical trials studying the use of SSRIs in youth (Cheung et al. 2005). Although not all trials described all aforementioned adverse events, aggression, agitation and/or behavioral activation were reported in the majority of the papers. The rates of these adverse events in the published studies range from 1 to 8 %. Only a small proportion (less than 10 %) of these events were classified as a 'serious adverse event' or led to discontinuation from the trials. In case reports of behavioral activation associated with SSRIs, these adverse events occurred in patients with comorbid diagnoses of anxiety or externalizing disorders and in patients who had good initial responses to the AD (Cheung et al. 2005). Behavioral activation generally developed within days to weeks after the start of AD treatment. In the majority of these cases, the symptoms also resolved shortly (within 4 weeks) after the lowering of the dosage or the discontinuation of the medication without addition an antipsychotic or a mood stabilizer. These adverse events also occurred at lower dosages. A recent meta-analysis reported activation symptoms strongly trended toward being associated with AD treatment (OR 1.86). To note, this meta-analysis did not include citalopram as one of the studied ADs (Strawn et al. 2015).

To date, we found no published studies regarding the influence of genes on SE profile in children. Pharmacogenetic approaches are particularly relevant in pediatric populations due to several reasons: first, most studies of the pharmacodynamics of ADs have been conducted in adults, making studies of the pharmacogenetics of SSRI in children scarce (Blazquez et al. 2012). Second, pharmacogenetic approaches are particularly relevant in pediatric populations because of concerns about the suicide risk of SSRIs, resulting in a black-box warning. There is great hope that in the future it will be possible to personalize psychiatric treatments based on genetic profiles and thus moderate this high-risk in pediatric population.

Till now, there is an unresolved debate regarding the serious phenomenon of SSRI-induced suicidality and its etiology, frequency and its relation to other SSRI-induced SE's (Amitai et al. 2015). There is controversy in the literature regarding the association between suicidality, mainly, suicidal ideation and not complete suicide, and impulsive–aggressive behaviors (IABs) associated with SSRIs; some researchers believe that the use of SSRIs is linked with outbursts of anger and aggression and these are, in fact, related to suicidality, while others believe that suicidality and aggression are two distinct phenomena. According to the first school, IABs are regarded as possible suicide intermediate phenotypes, mediating the relationship between genes and suicide outcome. Suicide is thought to result from the interaction of different factors. Among these, substantial work has pointed to the role of IABs increasing suicide risk (Zouk et al. 2007). As IABs are heritable (Seroczynski et al. 1999), exist independently from suicidal behavior, cosegregate in families with suicidal behavior and seem to increase recurrence of suicidal behavior in relatives of probands selected for high levels of

IABs (Brent et al. 1996; Johnson et al. 1999; Kim et al. 2005; Popova 2006). It has been suggested that IABs are suicide intermediate phenotypes. As such, IABs would mediate either directly or indirectly, the association between genetic factors and suicide outcome (Van Praag 2000).

In adults, it was shown that the HTR2A CC genotype (rs6313) was strongly associated with discontinuation due to intolerance in patients treated with paroxetine (Murphy et al. 2003). Recently, Hofer et al. investigated polymorphisms in the 5-HTR1A and 5-HTR2A genes, including rs6313, and found no association between them and suicide risk (Hofer et al. 2016).

In this prospective open treatment trial of citalopram for pediatric anxiety and/or depression, we investigated a possible correlation between citalopram adverse events and several candidate genes related to the serotonergic system. In contrast to Murphy et al's findings (Murphy et al. 2003), we did not find the HTR2A CC genotype related to the SE profile of citalopram in children. Our most interesting finding was that 5-HTR1Dβ polymorphism (rs6296) was positively associated with irritability, i.e., subjects with the CC genotype showed higher levels of agitation as opposed to subjects with the CG/GG genotype. We found no association between this polymorphism and elevated mood or elevated anxiety, which are also considered part of the constellation of symptoms known as behavioral activation (Amitai et al. 2015).

The 5-HTR1Dβ gene is located on the long arm of chromosome 6. A studied 5-HTR1Dβ single base G/C substitution at nucleotide 861 in the coding region (rs6296) is synonymous, i.e., this substitution does not change amino acid (Val287Val). Nevertheless, the synonymous variant may be important too, if the SNP is located in linkage disequilibrium with functional polymorphism or causes functional RNA structure changes for example (Nackley et al. 2006).

Considering the important role of 5-HTR1Dβ receptors in the control of serotonin release, and given that serotonin is one of the major neurotransmitters involved in the regulation of behavior, this polymorphism could provide a valuable tool for studying genetic linkage of the 5-HTRlDβ receptor gene to various disorders in which serotonin is postulated to be involved. Of note, several pharmacological studies exclude a direct involvement of the 5-HTRlDβ receptor in the pathogenesis of bipolar disorder (Mundo et al. 2001), which may highly relate to SSRI side effects (Strawn et al. 2014). Further investigations combining genetic and pharmacological strategies are warranted.

Thus, our study suggests an intermediate phenotype between citalopram induced suicidality and aggression, via agitation SE. Our results also indicate that pharmacodynamic effects such as receptor variation can be more important than pharmacokinetic factors. We expected patients with genotypes encoding impaired metabolism to show more severe adverse events and more discontinuations.

Limitations

This study has several limitations, shared with other pharmacogenetic investigations. Among them are the relatively small sample size, the lack of a placebo arm, the open-label nature of the study and the potential for population stratification. There was no pharmacological documentation of adherence or drug concentration, so that nonresponse could be misattributed to genotype when it could be due to lack of adherence or rapid clearance. Unfortunately, we did not measure citalopram blood concentrations and we did not assess the influence of SNPs in genes encoding for oxidative enzymes which may affect the drugs' concentration. More SNPs should be screened to avoid false negative findings (see, for instance Altar et al. 2015). It is of note that SSRIs have a common mechanism of serotonergic action but they are different medications in terms of their pharmacodynamic and pharmacokinetic characteristics, and thus, our results are relevant only to citalopram treatment and cannot be generalized to all SSRIs.

Conclusion

Our results indicate that a variation in the 5-HTR1Dβ gene (CC genotype) may be important in the vulnerability to develop agitation/activation as SE of citalopram treatment in children and adolescents with MDD/dysthymia and/or anxiety disorders. It has been suggested that agitation/activation and suicidal behavior are intermediate phenotypes. As such, emergence of agitation/agitation may mediate either directly or indirectly, the association between genetic factors and suicidal behavior in citalopram treated children. Nevertheless, 5-HTR1Dβ polymorphism may be a risk genetic marker of aggression and agitation adverse events in children and adolescents with depression and/or anxiety treated with citalopram. If confirmed, it might be possible to identify patients who are at risk and avoid citalopram treatment or to administer lower doses in an attempt to diminish the risk of iatrogenic agitation. Moreover, if replicated, the finding may help in understanding the mechanism of agitation/activation in response to citalopram and lead to treatment strategy which may reduce the rate of this harmful adverse effect.

References

Adegbite-Adeniyi C, Gron B, Rowles BM, Demeter CA, Findling RL (2012) An update on antidepressant use and suicidality in pediatric depression. Expert Opin Pharmacother 13(15):2119–2130

Altar CA, Carhart JM, Allen JD, Hall-Flavin DK, Dechairo BM, Winner JG (2015) Clinical validity: combinatorial pharmacogenomics predicts antidepressant responses and healthcare utilizations better than single gene phenotypes. Pharmacogenom J 15(5):443–451

Amitai M, Chen A, Weizmann A, Apter A (2015) SSRI-induced activation syndrome in children and adolescents—what is next? Curr Treat Options Psychiatry 2(1):28–37

Bernstein GA, Shaw K (1997) Practice parameters for the assessment and treatment of children and adolescents with anxiety disorders. American Academy of Child and Adolescent Psychiatry. J Am Acad Child Adolesc Psychiatry 36(10 Suppl):69S–84S

Birmaher B, Khetarpal S, Brent D, Cully M, Balach L, Kaufman J, Neer SM (1997) The screen for child anxiety related emotional disorders (SCARED): scale construction and psychometric characteristics. J Am Acad Child Adolesc Psychiatry 36:545–553

Birmaher B, Brent DA, Benson RS (1998) Summary of the practice parameters for the assessment and treatment of children and adolescents with depressive disorders. American Academy of Child and Adolescent Psychiatry. J Am Acad Child Adolesc Psychiatry 37(11):1234–1238

Birmaher B, Brent DA, Chiappetta L, Bridge J, Monga S, Baugher M (1999) Psychometric properties of the screen for child anxiety related emotional disorders (SCARED): a replication study. J Am Acad Child Adolesc Psychiatry 38:1230–1236

Blazquez A, Mas S, Plana MT, Lafuente A, Lázaro L (2012) Fluoxetine pharmacogenetics in child and adult populations. Eur Child Adolesc Psychiatry 21:599–610

Brent DA, Bridge J, Johnson BA, Connolly J (1996) Suicidal behavior runs in families. A controlled family study of adolescent suicide victims. Arch Gen Psychiatry 53(12):1145–1152

Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, Ren L, Brent DA (2007) Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA 297(15):1683–1696

Brummett BH, Babyak MA, Jiang J, Shah SH, Becker RC, Haynes C, Chryst-Ladd M, Craig DM, Hauser ER, Siegler IC, Kuhn CM, Singh A, Williams RB (2013) A functional polymorphism in the 5HTR2C gene associated with stress responses also predicts incident cardiovascular events. PLoS One 8(12):1–7

Cheung AH, Dewa CS, Levitt AJ (2005) Clinical review of mania, hostility and suicide-related events in children and adolescents treated with antidepressants. Paediatr Child Health 10(8):457–463

Clark SL, Adkins DE, Aberg K, Hettema JM, McClay JL, Souza RP, van den Oord EJCG (2012) Pharmacogenomic study of side-effects for antidepressant treatment options in STAR*D. Psychol Med 42:1151–1162

Gibbons RD, Brown CH, Hur K, Davis J, Mann JJ (2012) Suicidal thoughts and behavior with antidepressant treatment: reanalysis of the randomized placebo-controlled studies of fluoxetine and venlafaxine. Arch Gen Psychiatry 69(6):580–587

Guy W (1976) Clinical global improvement scale. Assessment manual of psychopharmacology. National Institute of Mental Health, Rockville (Maryland)

Hammad TA, Laughren T, Racoosin J (2006) Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 63(3):332–339

Hofer P, Schosser A, Calati R, Serretti A, Massat I, Kocabas NA, Konstantinidis A, Mendlewicz J, Souery D, Zohar J, Juven-Wetzler A, Montgomery S, Kasper S (2016) The impact of serotonin receptor 1A and 2A gene polymorphisms and interactions on suicide attempt and suicide risk in depressed patients with insufficient response to treatment—a European multicentre study. Int Clin Psychopharmacol 31(1):1–7. doi:10.1097/YIC.0000000000000101

Johnson JG, Cohen P, Skodol AE, Oldham JM, Kasen S, Brook JS (1999) Personality disorders in adolescence and risk of major mental disorders and suicidality during adulthood. Arch Gen Psychiatry 56(9):805–811

Kato M, Serretti A (2010) Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder. Mol Psychiatry 15(5):473–500

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N (1997) Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 36:980–988

Kim CD, Seguin M, Therrien N, Riopel G, Chawky N, Lesage AD, Turecki G (2005) Familial aggregation of suicidal behavior: a family study of male suicide completers from the general population. Am J Psychiatry 162(5):1017–1019

Kirchheiner J, Nickchen K, Bauer M, Wong ML, Licinio J, Roots I, Brockmöller J (2004) Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. Mol Psychiatry 9(5):442–473

Kronenberg S, Apter A, Brent DA, Schirman S, Melhem N, Pick N, Gothelf D, Carmel M, Frisch A, Weizman A (2007) Serotonin transporter polymorphism (5-HTTLPR) and citalopram effectiveness and side effects in children with depression and/or anxiety disorders. J Child Adolesc Psychopharmacol 17(6):741–750

Lappalainen J, Dean M, Charbonneau L, Virkkunen M, Linnoila M, Goldman D (1995a) Mapping of the serotonin 5-HT1D beta autoreceptor gene on chromosome 6 and direct analysis for sequence variants. Am J Med Genet 60(2):157–161

Lappalainen J, Zhang L, Dean M, Oz M, Ozaki N, Yu DH, Virkkunen M, Weight F, Linnoila M, Goldman D (1995b) Identification, expression, and pharmacology of a Cys23-Ser23 substitution in the human 5-HT2c receptor gene (HTR2C). Genomics 27(2):274–279

Lohoff FW, Ferraro TN (2010) Pharmacogenetic considerations in the treatment of psychiatric disorders. Expert Opin Pharmacother 11(3):423–439

Maddox JC, Levi M, Thompson C (1994) The compliance with antidepressants in general practice. J Psychopharmacol 8(1):48–52

Mundo E, Zai G, Lee L, Parikh SV, Kennedy JL (2001) The 5HT1Dbeta receptor gene in bipolar disorder: a family-based association study. Neuropsychopharmacology 25(4):608–613

Murphy GM, Kremer C, Rodrigues HE, Schatzberg AF (2003) Pharmacogenetics of antidepressant medication intolerance. Am J Pschicatry 160:1830–1835

Nackley AG, Shabalina SA, Tchivileva IE, Satterfield K, Korchynskyi O, Makarov SS, Maixner W, Diatchenko L (2006) Human catechol-O-methyltransferase haplotypes modulate protein expression by altering mRNA secondary structure. Science 314:1930–1933

Papakostas GI (2009) Managing partial response or nonresponse: switching, augmentation, and combination strategies for major depressive disorder. J Clin Psychiatry 70(Suppl 6):16–25

Popova NK (2006) From genes to aggressive behavior: the role of serotonergic system. BioEssays 28(5):495–503

Poznanski E, Freeman LN, Mokros HB (1985) Children's depression rating scale-revised. Psychopharmacol Bull 21:979–989

Qin B, Zhang Y, Zhou X, Cheng P, Liu Y, Chen J, Fu Y, Luo Q, Xie P (2014) Selective serotonin reuptake inhibitors versus tricyclic antidepressants in young patients: a meta-analysis of efficacy and acceptability. Clin Ther 36(7):1087–1095

Rotberg B, Kronenberg S, Carmel M, Frisch A, Brent D, Zalsman G, Apter A, Weizman A (2013) Additive effects of 5-HTTLPR (serotonin transporter) and tryptophan hydroxylase 2 G-703T gene polymorphisms on the clinical response to citalopram among children and adolescents with depression and anxiety disorders. J Child Adolesc Psychopharmacol 23(2):117–122

Schirman S, Kronenberg S, Apter A, Brent DA, Melhem N, Pick N, Carmel M, Frisch A, Weizman A, Gothelf D (2010) Effectiveness and tolerability of citalopram for the treatment of depression and anxiety disorders in children and adolescents: an open-label study. J Neural Transm 117:139–145

Seroczynski AD, Bergeman CS, Coccaro EF (1999) Etiology of the impulsivity/aggression relationship: genes or environment? Psychiatry Res 86(1):41–57

Serretti A, Artioli P (2004) The pharmacogenomics of selective serotonin reuptake inhibitors. Pharmacogenomics J 4(4): 233–244

Shanee N, Apter A, Weizman A (1997) Psychometric properties of the K-SADS-PL in an Israeli adolescent clinical population. Isr J Psychiatry Relat Sci 34:179–186

Souery D, Oswald P, Massat I, Bailer U, Bollen J, Demyttenaere K, Kasper S, Lecrubier Y, Montgomery S, Serretti A, Zohar J, Mendlewicz J (2007) Clinical factors associated with treatment resistance in major depressive disorder: results from a European multicenter study. J Clin Psychiatry 68(7):1062–1070

Strawn JR, Adler CM, McNamara RK, Welge JA, Bitter SM, Mills NP, Barzman DH, Cerullo MA, Chang KD, Strakowski SM, DelBello MP (2014) Antidepressant tolerability in anxious and depressed youth at high risk for bipolar disorder: a prospective naturalistic treatment study. Bipolar Disord 16(5):523–530

Strawn JR, Welge JA, Wehry AM, Keeshin B, Rynn MA (2015) Efficacy and tolerability of antidepressants in pediatric anxiety disorders: a systematic review and meta-analysis. Depress Anxiety 32(3):149–157

Van Praag HM (2000) Serotonin disturbances and suicide risk: is aggression or anxiety the interjacent link? Crisis 21(4):160–162

Warren JT, Peacock ML, Rodriguez LC, Fink JK (1993) An MspI polymorphism in the hyman serotonin receptor gene (HTR2): detection by DGGE and RFLP analysis. Hum Mol Genet 2(3):338

Zouk H, McGirr A, Lebel V, Benkelfat C, Rouleau G, Turecki G (2007) The effect of Genetic variation of the serotonin 1B receptor gene on impulsive aggressive behavior and suicide. Am J Med Genet B Neuropsychiatr Genet 144B(8):996–1002