Effects of Persisting Emotional Impact from Child Abuse and Norepinephrine Transporter Genetic Variation on Antidepressant Efficacy in Major Depression: A Pilot Study

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Objective: Previous studies suggest child abuse and serotonergic polymorphism influence depression susceptibility and anti-depressant efficacy. Polymorphisms of the norepinephrine transporter (NET) may also be involved. Research in the area is possibly clouded by under reporting of abuse in researcher trials.

Methods: Adults (n=51) with major depressive disorder has 8 weeks treatment with escitalopram or venlafaxine. Abuse history was obtained, the ongoing emotional impact of which was measured with the 15-item impact of event scale (IES-15). The 17-item Hamilton Depression Rating Scale (HDRS) was applied serially. Two *NET* polymorphisms (rs2242446 and rs5569) were assayed, blinded to HDRS ratings and abuse history.

Results: No subjects reporting abuse with high impact in adulthood (IES-15 ≥26, n=12) remitted; whereas 77% reporting low impact (IES-15 <26; n=26) remitted (p<0.001). Subjects reporting high impact abuse (n=12) had a 50-fold (95% confidence interval=4.85-514.6) greater odds of carrying rs2242446-TT genotype, but the small sample size leaves this finding vulnerable to type I error.

Conclusion: The level of persisting impact of child abuse appears relevant to antidepressant efficacy, with susceptibility to such possibly being influence by *NET* rs2242446 polymorphism. Larger studies may be merited to expand on this pilot level finding given potential for biomarker utility.

KEY WORDS: Abuse; Child; Antidepressants; Norepinephrine transporter; Remission.

INTRODUCTION

Prediction of antidepressant response has been an elusive goal.[1] Several studies have investigated the relationship between a history of child abuse and differential antidepressant response in adults suffering from major depression.[2-8] Findings have been mixed. In the largest study to date[6] 808 patients suffering chronic major depressive disorder (MDD) with clinically significant child abuse (assayed with a trauma questionnaire) had lower response rates to antidepressants. Nemeroff *et al.*[3] studied 681 patients with chronic MDD, with a trauma scale and number of abuse events used to help grade abuse severity. They found that subjects with a history of significant child abuse had preferential response to psychotherapy over the antidepressant nefazodone, with combined treatment not superior to psychotherapy alone. In yet another study, no significant differences in remission rates was identified among 312 adults randomized to interpersonal psychotherapy or selective serotonin reuptake inhibitor, but results were not stratified by abuse severity.[7] Finally, among 195 outpatients with MDD a history of child abuse did not help predict response to fluoxetine or nortriptyline.[5] A recent meta-analysis[9] of the above and other studies concluded that subjects not reporting child abuse had a better response rate to antidepressants (odds ratio=1.43, 95% conference interval [CI] 1.11-1.83). However none of these studies assayed the current emotional impact from prior child abuse. It is possible that the ongoing emotional salience of child abuse in adulthood may be the mediating fac-

tor to antidepressant efficacy, in turn possibly mediated by susceptibility polymorphisms.

Emotionally impactful child abuse lacks uniform definition[10,11] limiting research in the role of ongoing emotional impacts of abuse into differential antidepressant efficacy and susceptibility genes. Other methodological challenges affect investigating the role of ongoing impacts from child abuse to differential antidepressant efficacy and susceptibility polymorphisms. It is less likely a patient will disclose abuse history to somebody they have not established a trusting alliance with, making the baseline seeking of such personal information prone to false negative reports (Hanson *et al.*,[12] Roesler and Wind[13]). This may limit the sensitivity of asking about child abuse as a response predictor from outset of treatment. Additionally, asking about childhood abuse at baseline may act as a psychological stressor for those with such a history, potentially affecting antidepressant response confounding investigation.[14-17]

Only a proportion of abused children suffer mental illness in adulthood.[18-21] Various protective psychosocial factors have been implicated including personality style, emotional self-regulation, secure attachment relationships, and community supports.[20,22,23] Individual features such as personality style and genetic profile may also influence individual resilience or susceptibility to trauma. Investigation of gene environment interactions have demonstrated that childhood trauma is a strong environmental 'pathogen' that may be moderated by genetic variation, most notably the serotonin transporter linked promoter region (5HTTLPR) polymorphism.[18,24-33] A recent meta-analysis of 52 studies (n=40,749) concluded there is "strong evidence" that the s allele of 5HTTLPR significantly elevated the "depressogenic" effects of childhood maltreatment.[34] It is possible a confluence of genetic susceptibilities will moderate the influence of childhood trauma on adult psychopathology beyond the 5HTTLPR polymorphism.[35] It is possible that such genetic variability between siblings exposed to similar environmental stressors and resources in part may explain variability in mental health outcomes among them.[36] Such vulnerability biomarkers could one day assist targeting resources to children more susceptible to adverse adult outcomes, making this question of potential clinical translational value.

Beyond 5HTTLPR genotype, various other genes spanning monoaminergic, inflammatory, and neurotrophic related systems have also been implicated in trauma vulnerability, all be it not yet to a meta-analytic level of evidence.[37] Despite the monoamine hypothesis of MDD

initially highlighting the role of norepinephrine[38] to date little empirical investigation has focussed on the role of norepinephrine transporter (*NET*) polymorphisms influencing vulnerability to child abuse produce adulthood psychopathology.[39] This is surprising given the norepinephrine appears to have a key role in stress responses.[40] Studies have demonstrated increased urinary norepinephrine metabolite excretion in both adults and youth who have been exposed to abuse, but findings are inconsistent.[41-43]

NET is a sodium dependent transporter re-uptaking norepinephrine into the neuron for both cyclic use and termination of the action of norepinephrine at the synapse.[44-46] Recently, chronic stress has been shown to up-regulate *NET* gene expression in rats.[47] Human studies have yet to be reported.[40] The promoter region of the *NET* gene is approximately 4.7 kb in length and contains an additional 476 base pair intron containing several potential transcriptional elements.[48] The NET182 polymorphism (rs2242446) located in this *NET* promoter region appears to alter transcription.[49] Additionally, a synonymous NET G1287A polymorphism (rs5569) in exon 6 has been linked to alternative mRNA splicing and reduced NET functioning,[50] and has also been associated with differential response to noradrenergic antidepressants.[51-53] Furthermore, recently the combination of a child abuse history and carrying the TT polymorphism at rs5569 was demonstrated to significantly decreased antidepressant response in a sample of 308 patients,[54] and appears commonly polymorphic rather than being a rare variant of limited public health clinical utility.[55,56]

The primary a priori study hypothesis was that subjects with persisting high level emotional impact from child abuse exposure (high or low emotional impact assayed with the 15-item impact of event scale [IES-15]) would have reduced antidepressant efficacy. Secondarily − on a *post hoc* − basis we examine whether two *NET* polymorphisms (rs2242446 and rs5569) helped predict antidepressant efficacy stratifying by child abuse history and level of persisting emotional impact. Finally, on a *post hoc* basis we sought to investigate whether the level of persisting emotional impact from child abuse into adulthood (high or low impact) was associated with *NET* rs2242446 or rs5569 polymorphisms.

METHODS

Subjects and Ratings

Patients 18 years and over with a principal diagnosis of

MDD (Diagnostic and Statistical Manual of Mental Disorders 4th edition [DSM-IV] criteria, semi-structured clinical interview) and baseline HDRS ≥18 were included in the study and studied prospectively for 8 weeks. Treatment refractory cases (≥3 failed medication trails) were excluded as were subjects with co-morbid physical of psychiatric illnesses and those pregnant or breast feeding. Alternative care may have been more appropriate for such patients. There was a five half-life drug washout period for subjects already taking an antidepressant. The study was a limb of a larger study,[57,58] with one of the recruitment sites (n=51) obtaining a history of child abuse and rating ongoing emotional impacts with the IES-15. High impact abuse was defined as IES-15 score ≥ 26 following the scale's validated scoring instructions.[59] Clinical Global Impression (CGI) scales for improvement and severity were used to guide clinical dose adjustment.[60] All ratings were blinded to genotype, and history of child abuse was assessed at the end of the trial such that HDRS ratings were blind to history of child abuse, and in hopes disclosure rates would be better, and that treatment response would not be confounded by emotional distress reactions from being asked their child abuse history. During the first week all patients received a standard dose of either escitalopram (ESC) 10 mgs or venlafaxine (VEN) 75 mgs. ESC or VEN allocation was on the basis of clinical preference.[61] At weeks 1, 4, and 8 of treatment doses were adjusted on a clinical basis, with the dose escalated if there was no improvement on the CGI scale, or the dose reduced if problematic side effects emerged (elevation of the UKU side effects scale with patient intolerance of the reported side effect).[62] No other psychotropic medications were given and psychotherapy was not commenced during the study period. The study was approved by an independent research ethics committee (Study 138, The Melbourne Clinic, Richmond, Australia).

Genotyping

DNA was extracted from each sample using QIAamp DNA Mini Kit (QIAGEN Inc., Hilden, Germany) from venous blood or buccal brush samples. Genotypes of candidate (*NET* rs2242446 and rs5569) and potential confounding (CYP2D6 and CYP2C19 metaboliser status; *ABCB1* [P-glycoprotein] rs1045642; and 5HTTLPPR *s* and *l*) polymorphisms[63] were determined by the polymerase chain reaction followed by single primer extension and analysis on a Sequenom® Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry

(MALDI-TOF; Sequenom Inc., San Diego, CA, USA) 384 well genetic analysis system.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics software ver. 19.0 (IBM Co., Armonk, NY, USA). Intention-to-treat analysis was applied. Demographic variables by abuse exposure and impact were examined using Fisher's exact test and *t*-tests for categorical and continuous variables respectively. Repeated-measures analysis of variance (ANOVA) was used to determine changes in HDRS scores over the 8-weeks of treatment by abuse exposure and impact as well as *NET* genotype. Genotype frequencies by abuse exposure and emotional impacts in adulthood were examined using a chi-square analysis with a Bonferroni correction ($p=0.025$) for the two *NET* candidate polymorphisms. The CubeX program was applied to detect departures from Hardy Weinberg Equilibrium (HWE) and estimate pairwise linkage disequilibrium (LD) measures r^2 and D'.[64] Polymorphisms with HWE greater than 0.01 were considered to be in equilibrium. LD was assumed if both *NET* polymorphisms had r^2 and D' values greater than 0.80. This information would guide the need for haplotype analysis.

RESULTS

No less than 38 (74.5%) of the 51 subjects interviewed for child abuse history at week 8 reported exposure to child abuse (physical, sexual, or emotional). Only 12 (31.6%) of the subjects reporting a history of child abuse had persisting marked emotional impacts (high impact group) from it (IES-15 mean 37.2, standard deviation [SD]=6.8). The other 26 subjects reporting child abuse had much lower scores on the IES-15 (mean=11.2, SD=8.2) suggesting the abuse did not have persisting emotionally impacts into adulthood (low impact group).

Characteristics of subjects by child abuse exposure, level of impact, and *NET* genotype are displayed in Table 1. Subjects not reporting exposure to child abuse had greater baseline HDRS scores compared to subjects in the high impact exposed group ($p=0.043$), but there was no significant difference in baseline HDRS between the low and high impact groups. Subjects in the high impact group were less likely to have tertiary level education compared to the low impact ($p=0.018$) group. No differences were observed by *NET* genotype stratified by abuse history and impact.

Table 1. Characteristics of sample by exposure to child abuse and its impact in adulthood

Characteristic	Not exposed (n=13)	Exposed			NET rs2242226		
		Low impact (n=26)	High impact (n=12)	Pairwise differences*	CC/TC (n=30)	TT (n=21)	Pairwise differences*
Baseline HDRS	25.9±5.7	24.0±3.9	21.5±3.4	Low>High	24.6±4.8	22.9±4.0	–
Duration of depression (year)	6.6±4.5	5.2±3.3	8.0±5.6	–	5.5±3.9	7.2±4.7	–
Age (year)	38.2±11.4	43.1±15.6	43.8±11.2	–	43.9±15.0	39.3±11.0	–
Male	23.1 (3)	42.3 (11)	41.7 (5)	–	46.7 (14)	23.8 (5)	–
Tertiary education	53.8 (7)	61.5 (16)	25.0 (3)	Low>High	56.7 (17)	42.9 (9)	–
Employed	100 (13)	96.2 (25)	100 (12)	–	96.7 (29)	100 (21)	–
Medication							
Venlafaxine	46.2 (6)	42.3 (11)	58.3 (7)	–	46.7 (14)	47.6 (10)	–
Escitalopram	53.8 (7)	57.7 (15)	41.7 (5)	–	53.3 (16)	52.4 (11)	–
Venlafaxine dose at 8 weeks (mg)	187.5±78.7	150.0±82.2	203.6±36.6	–	160.7±77.0	195.0±63.2	–
Escitalopram dose at 8 weeks (mg)	24.3 (7.7)	22.7 (7.0)	22.0 (10.9)	–	23.1 (7.0)	22.7 (9.0)	–
ABCB1 rs1045642-TT carrier	30.8 (4)	34.6 (9)	25.0 (3)	–	36.7 (11)	23.8 (5)	–
CYP2C19 extensive metaboliser	84.6 (11)	65.4 (17)	75.0 (9)	–	70.0 (21)	76.2 (16)	–
CYP2D6 extensive metaboliser	61.5 (8)	65.4 (17)	66.7 (8)	–	63.3 (19)	66.7 (14)	–
5HTTLPR l allele carrier	84.6 (11)	84.6 (22)	83.3 (10)	–	76.6 (23)	85.7 (18)	–

Values are presented as mean±standard deviation or percent (number).
*Significant at $p<0.05$.

Effects of Child Abuse Exposure and Persisting Emotional Impacts on Antidepressant Efficacy

Subjects with no abuse history and low impact abuse had significantly greater HDRS score reduction ($p=0.001$) compared to subjects with high impact abuse during 8 weeks of antidepressant treatment (Fig. 1). Total of 52.6% of subjects reporting child abuse were in remission (HDRS≤7) from MDD at 8 weeks, whereas 92.3% of subjects without a history of child abuse were in remission from MDD at 8 weeks ($p=0.01$). Stratification of remission rates by abuse impact revealed subjects with high impact abuse had a zero rate of remission from MDD, while 77% of subjects with low impact abuse remitted ($p<0.001$). Statistical adjustment for tertiary education did not have an effect on these findings.

Effects of Child Abuse and NET Genotype on Antidepressant Efficacy

The rs2242226 and rs5569 polymorphisms were not in linkage disequilibrium (D'=0.13, r^2=0.02) and neither polymorphism was associated with remission or symptom reduction in the full sample. However, we did observe a non-significant trend for rs2242226 in which C-carriers had greater symptom reduction over 8 weeks antidepressant treatment (F=2.98, degree of freedom [df]=3, $p=0.071$) but were not more likely to remit (chi-square=1.64, df=1, $p=0.162$). Subjects reporting a history of child abuse were less likely to have rs2242226 TT genotype compared to subjects reporting no abuse history (24% vs. 92%, $p<0.001$). Subjects reporting high impact abuse had a
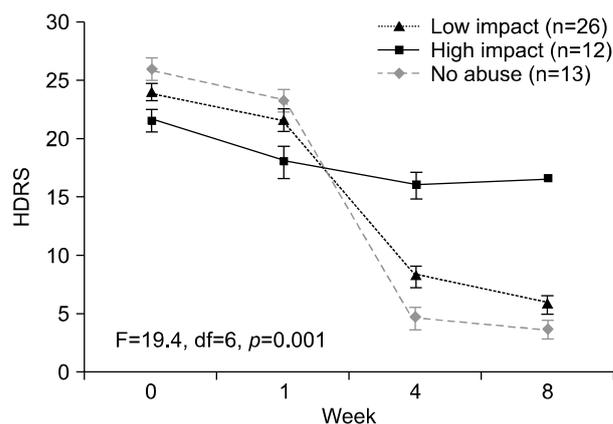

Fig. 1. Seventeen-item Hamilton Depression Rating Scale (HDRS) score change over 8 weeks antidepressant treatment stratified by abuse history and level of persisitng emotional impacts. Subjects with no abuse history and low impact abuse had significantly greater HDRS score reduction ($p=0.001$) compared to subjects with high impact abuse.
df, degree of freedom.

50-fold (95% CI=4.85-514.6) greater odds of being TT genotype at rs2242226 compared to those reporting low impacts abuse (Fig. 2).

Among subjects reporting exposure to child abuse (n=38), C carriers at rs2242226 had greater symptom reduction over the 8 weeks of treatment compared to TT carriers ($p=0.001$; Fig. 3). However, symptom reduction for C carriers reporting high impact abuse was attenuated; albeit reductions remained greater than that observed for TT carriers with either high or low impact abuse ($p<0.001$; Fig. 4). No interaction effects between the other *NET*
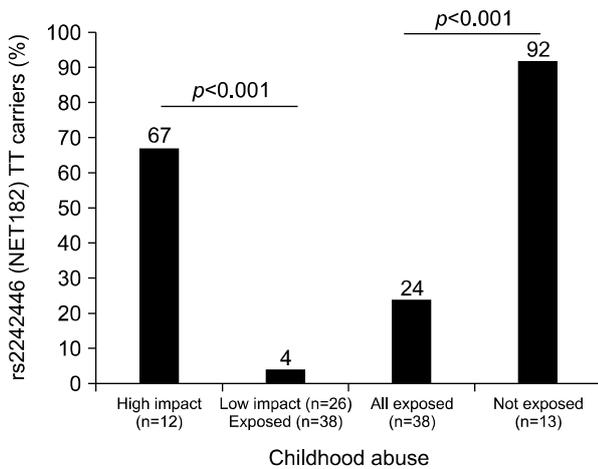
Fig. 2. Proportions of TT carriers at rs2242446 (NET182) stratified by exposure to child abuse and level of persisting emotional impact. Subjects reporting high impact abuse had a 50-fold (95% confidence interval=4.85-514.6) greater odds of being TT genotype at rs2242226 compared to those reporting low impacts abuse.

Fig. 3. Seventeen-item Hamilton Depression Rating Scale (HDRS) score over 8 weeks antidepressant treatment stratified by rs2242226 (NET182) genotype among subjects with a history of child abuse. C carriers at rs2242226 had greater symptom reduction over the 8 weeks of treatment compared to TT carriers (p=0.001).
df, degree of freedom.

Fig. 4. Seventeen-item Hamilton Depression Rating Scale (HDRS) score change over 8 weeks antidepressant treatment among subjects reporting a history of child absue stratified by rs2242226 (NET182) genotype and level of persisting emotional impact from child abuse.
df, degree of freedom.

polymorphism investigated (rs5569) and child abuse was identified.

DISCUSSION

This study demonstrates an association between child abuse history and poorer remission rates to the antidepressants ESC and VEN－particularly for subjects for whom child abuse remained highly emotionally impactful in adulthood (IES-15≥26). The study also suggests a *NET* functional polymorphism increases the risk of child abuse remaining highly emotionally impactful into adulthood (TT genotype at rs2242226). Other potential gene environment associations have been reported, but none for a polymorphism located in the *NET* gene.[37]

Our finding that individuals reporting high impact abuse had greater odds of being TT carriers at rs2242226 is biologically plausible. The recent finding that chronic stress up-regulates *NET* expression in animals[47] suggests impediments to such up-regulation may prevent normal allostatic adjustment.[65] Increased DNA methylation from environmental stress appears to impede gene transcription[66-70] and seems to be a mechanism mediating gene environment interactions in depression.[71] As the rs2242226 polymorphism is in a promoter region[49] it may have an additive effect on reduced *NET* expression in the setting of stress induced *NET* hyper-methylation, with TT carriers potentially being particularly susceptible to *NET* under expression when exposed to environmental stress. This may underlie both reduced antidepressant efficacy and an
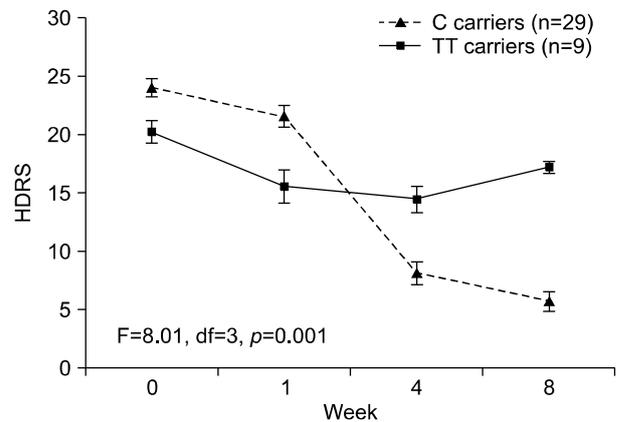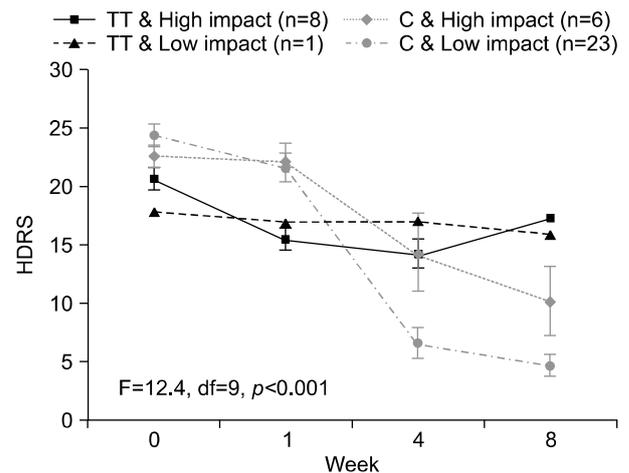
elevated risk of persisting emotional impacts from child abuse among such subjects - possibly akin to the association found for *s* carriers at the 5HTTLPR.[34,72] While our study design could not shed light on whether the rs2242226 TT genotype increased the risk of *de novo* MDD, it did demonstrate that subjects reporting high impact abuse who also carried the TT genotype had poorest response to antidepressant medication. A converse finding that T carriers at rs2242226 with MDD had better re-

sponse to the antidepressant milnacipran[52] has been reported; however, this study failed to control for child abuse history or impacts possibly confounding results. In fact, in the current study 12 of the 13 subjects reporting no exposure to child abuse carried the TT genotype of which 92% (n=11) remitted. Thus, it seems the detrimental effect of the TT genotype appears to be dependent on child abuse exposure, suggesting a gene-environment interaction. Larger studies will be required to confirm this preliminary gene-environment association between *NET* rs2242226 and persisting emotional impacts from child abuse into adulthood, and to what extent this gene-environment association predicts antidepressant efficacy.

This study also provides an arguably more refined approach to assaying the clinical relevance of a history of child abuse in clinical care. Subjects with high impact abuse had substantially poorer antidepressant remission, in fact none of these subjects remitted. A strength of the study was that remission was employed as a more robust and clinically relevant measure of antidepressant efficacy given that subjects who respond but do not remit are more likely to relapse, making remission rather than response the goal of treatment and the pathway to recovery from MDD.[73]

A key characteristic of this study was that the information about child abuse was collected after the acute treatment phase in hopes to reduce false negative reports of child abuse, and also to prevent an emotional reaction to the asking of abuse history confounding medication efficacy via an adjustment reaction overlay. The reduced false negative report of child abuse may help explain the very high rates of child abuse reported by subjects in this study (74.5% of subjects). Alternatively, this high rate may reflect a concentration of such trauma in complicated MDD cases being managed in a psychiatric clinic form whence subjects were recruited. A limitation of this approach (history of abuse attained after 8 weeks treatment) is that our data cannot shed light on the role of child abuse reported prior to treatment as an antidepressant remission predictive factor. However, it may be the case in clinical practice that rapport is established over several weeks prior to considering an antidepressant trial, thus findings of this study could have some clinical translational utility－ subjects with impactful abuse less likely to benefit from an antidepressant making other modes of therapy for MDD potentially more appropriate.

The current study is limited by small sample size and lack of control for various polymorphisms (other than 5HTTLPR genotype) which have been implicated as

moderators of persisting emotional impacts from child abuse.[35] Having said this, controlling for 5HTTLPR genotype, pharmacokinetic related polymorphisms (P450 and ABCB1), medication dose, clinical features, demographic features, and ongoing impacts of child abuse with the IED-15 were novel strengths of this study.[33,63] Finally, variability between protective factors in childhood (e.g., community supports) could have also modified results, but these factors were not controlled for in this study, possibly confounding our findings.

One further limitation that needs to be considered is accuracy of diagnosis. Subjects were assessed in a semi-structured clinical interview by a psychiatrist to determine a principal diagnosis of MDD using DSM-IV criteria. It is possible that some subjects may have had features of conditions such as borderline personality disorder, post traumatic stress disorder, and adjustment disorder with depressed mood which did not meet clinical threshold for diagnosis and may have contributed to differential treatment outcome, potentially confounding our results. Sub-threshold personality disorder for example is likely to modulate treatment response,[74] but quantifying such sub-syndromal co-morbidities is difficult.

This is the first study to the authors' knowledge to suggest that the emotional impacts of child abuse in adulthood may be moderated by a *NET* polymorphism and those with persisting high emotional impacts from child abuse appear to have a significantly lower odds of remitting to antidepressant medication. If replicated in larger samples, these findings could help identifying children at higher risk of persisting emotional impacts from childhood abuse, possibly enabling better targeted supports and interventions to children subject to such trauma. These findings－if replicated－may also help guide prescribers throughout the decision making process on whether trialing an antidepressant in individuals with persistently emotionally impactful childhood trauma or other modalities of care are more appropriate.

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