

## ARE SSRI<sub>s</sub> RESPONSIBLE FOR PRECIPITATING SUICIDAL IDEATION IN TEENAGERS WITH 'SUBSYNDROMAL' BIPOLAR AFFECTIVE DISORDER WHO HAVE BEEN MISDIAGNOSED WITH UNIPOLAR DEPRESSION?

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### SUMMARY

Concerns have recently been raised about a possible link between suicidal ideation and the use of SSRIs in teenagers diagnosed with unipolar depression, such that the USA FDA and UK CSM have issued warnings regarding the use of SSRIs in adolescents with depression. We investigated this phenomenon first by recognizing that the initial presentation of unipolar and bipolar depression may only differ in subtle ways and with the result being that a significant number of patients are misdiagnosed at the expense of patient outcomes. This is especially pertinent as patients with bipolar disorder have increased lifetime rates of suicide as compared with those patients with unipolar depression. The normal developmental trajectory of bipolar disorder often involves recurrent depressive episodes in early adolescence before the development of hypomanic/manic episodes. Therefore, a misdiagnosis of bipolar disorder as unipolar depression in teenagers could explain the failure of SSRIs to adequately treat depressive episodes. A suboptimal response to SSRIs and so a lack of control of the depression is a risk factor for suicide. One reason for this suboptimal response is the markedly different neurotransmission involved in bipolar depression as compared to the neurotransmitter systems operated on by SSRIs. In bipolar disorder, dopamine is the principal neurotransmitter disrupted and we marshal structural, pharmacological and biochemical evidence to support this claim. One important strand of evidence involves polymorphisms in D1 and D2 dopamine receptors being implicated in the pathogenesis of bipolar affective disorder. Serotonin neurotransmission is affected by SSRIs, however the role of serotonin in bipolar disorder is much more ambiguous. The conclusion we arrive at is that the link between suicidality and SSRI use in adolescents diagnosed with unipolar depression may in fact be due to inappropriate treatment of misdiagnosed bipolar disorder that has yet to manifest with hypomanic/manic symptoms.

**Key words:** bipolar affective disorder - serotonin selective reuptake inhibitors (SSRIs) - unipolar depression - subsyndromal bipolar disorder - suicide

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### INTRODUCTION

In adolescents presenting with recurrent depressive episodes, it is clinically important to distinguish between an aetiology of unipolar depression or bipolar disorder. Subtle differences between the initial presentation of these two conditions result in a significant proportion of patients being misdiagnosed with unipolar depression (Smith et al. 2011, Chilakamarri et al. 2011). Unfortunately, this comes at the expense of patient outcomes since the management of these two conditions differs dramatically. Managing bipolar disorder as unipolar depression not only fails to improve symptoms but often worsens the condition by further destabilizing mood, increasing rapid cycling, and increasing the risk of alcohol and substance misuse as well as suicide (Nasrallah 2015).

This phenomenon may explain the failure of SSRIs in adolescents presenting with recurrent depressive episodes. Unipolar depression is primarily an illness of middle age compared to bipolar disorder which tends to present in adolescence, with an average age of onset six to ten years younger (Goodwin & Jamison 2007, Forty et al. 2008). Furthermore, subtleties in the character-

istics of bipolar depressive episodes compared to unipolar depressive episodes exist. The former displays more atypical depressive features, notably psychosis, agitation, suicidality, diurnal mood variation and hypersomnia (Cuellar et al. 2005). It also shows a greater number of depressive episodes which are of shorter duration (Furukawa et al. 2000, Goodwin & Jamison 2007, Rihmer 2007).

### THE NORMAL DEVELOPMENTAL TRAJECTORY OF BIPOLAR DISORDER

Moreover, considering the normal developmental trajectory of bipolar disorder supports the idea of adolescent recurrent depression representing the very first sign of bipolar disorder. It has been speculated that bipolar disorder evolves through a number of stages beginning in early adolescence. The normal trajectory often involves early non-specific disorders in childhood such as anxiety, followed by recurrent major depressive episodes in early adolescence before the final development of hypomanic/manic episodes (Duffy et al. 2010). Another study found that cyclothymic affective temperament was a strong predictor of future bipolar

transformation (and suicidality) in youngsters with first-episode major depression (Kochmann et al. 2005). Thus, it is plausible that adolescents presenting with recurrent depression are in fact following the normal trajectory of bipolar disorder but are yet to develop their first manic or hypomanic episode.

## SUICIDALITY AND THE USE OF SSRIs IN ADOLESCENTS

A major implication of this is the use of serotonin selective reuptake inhibitors (SSRIs) to treat patients who receive diagnoses of unipolar depression despite the fact that they may be presenting with 'subsyndromal' bipolar disorder, i.e. they have the neurobiological changes in keeping with bipolar disorder but have not yet presented with their first manic or hypomanic episode.

Recent concerns have been raised about a link between suicidality and the use of SSRIs in adolescents with major depressive disorder (Wohlfarth et al. 2006, Hammad et al. 2006, Whittington et al. 2004, Hetrick et al. 2004, Cox et al. 2012). Depression is a common disorder in adolescents (with a prevalence of 5.7% for 13-18 year olds) (Jane Costello et al. 2006) and is the main risk factor for suicide (Cox et al. 2012, Hawton et al. 2013). Furthermore, suicide is the third leading cause of death in adolescents (Anderson & Smith 2005). Disturbingly, adolescents with major depression are seven times more likely to complete suicide than those without major depression (Gould et al. 1998). Antidepressant use to treat depression can result in a variety of clinical responses whose categorisation includes optimal response, no response, worsening of depression (a 'covert switch' to an antidepressant-induced depressive mixed state that consists of intradepressive hypomanic symptoms), and the development of manic/hypomanic symptoms (an 'overt or manic switch') (Rihmer & Gonda 2011).

Although use of antidepressants reduces suicidality for unipolar major depressive disorder (Gibbons et al. 2012, Rihmer and Gonda 2013), antidepressants are associated with a suboptimal response in certain patient subgroups. Antidepressant-resistant depression and antidepressant-induced mixed state and manic switch are associated with a higher rate of antidepressant-associated suicidality as lack of sufficient control of depression is a risk factor (Rihmer 2007, Zisook et al. 2009). Adolescent patients are one of the subgroups in which antidepressant-associated suicide occurs more frequently and unsurprisingly there are also higher rates of antidepressant-resistant depression and antidepressant-induced manic switch (Baldessarini et al. 2005, Usala et al. 2008, Rihmer & Gonda 2011). This association was deemed dangerous enough that it resulted in the USA Food and Drug Administration to require the imposition of a black-box warning of this risk in 2004 and the UK Committee on Safety of Medicines to declare that the

risk-benefit profile of all SSRIs (except fluoxetine) as unfavourable in treating depression in adolescents.

However, it is crucial to understand the underlying causes for this higher rate of antidepressant-associated suicidality and increased vulnerability to antidepressant-resistant depression, antidepressant-induced mixed state and manic switches in adolescents.

## DOPAMINE TRANSMISSION

SSRIs have their anti-depressive effect by potentiating serotonin neurotransmission through inhibiting the serotonin transporter (SERT) and so preventing serotonin re-uptake (Kesić et al. 2012). However, in bipolar disorder, it is dopamine neurotransmission that is primarily disrupted in both the manic and depressive phases (Kato 2008). Multiple strands of evidence support this conclusion. That depression in bipolar disorder is caused by degeneration of dopamine neurons in the ventral tegmental area constitutes structural evidence (Torack & Morris 1988). Pharmacologically, mania is treated by antipsychotics through inhibiting dopamine neurotransmission and induced by psychostimulants through increasing it (Kato 2008). Biochemical evidence includes alteration of a metabolite of dopamine, homovanillic acid, in the cerebrospinal fluid (Goodwin & Jamison 2007). Animal models have also been utilised showing that aspects of the bipolar phenotype can be induced via dopaminergic mechanisms (Harrison 2016). Dopamine is also central to one theory that attempts to explain the manic and depressive phases of the illness (the 'dopamine dysfunction' hypothesis); it postulates that excessive activity of dopaminergic neurons results in mania, with the subsequent downregulation of dopamine receptors resulting in depression (Maletic & Raison 2014). The role of serotonin in bipolar disorder is much more ambiguous with ambivalent and conflicting evidence for its importance (Maletic & Raison 2014). So the central role of dopamine, as opposed to serotonin, neurotransmission in bipolar disorder may explain the modest efficacy of SSRIs as a treatment for adolescents who are developing this condition (Rihmer & Gonda 2011, Goodwin 2009).

## POLYMORPHISMS RELATED TO DOPAMINE TRANSMISSION

Furthermore, polymorphisms in the DRD1 gene encoding the D1 dopamine receptor have been implicated in the pathogenesis of bipolar affective disorder (Severino et al. 2005). A meta-analysis of patients with an A48G substitution in the DRD1 receptor was shown to be linked with bipolar disorder and not schizophrenia (Yao et al. 2013) indicating that dopamine plays a significant role in the development of bipolar affective disorder and that it is thus a neurotransmitter that can be linked to suicidal ideation. Furthermore, polymorphisms in the DAT1 gene (encoding a dopamine transporter)

and its promoter have been linked to the pathogenesis of bipolar disorder (Huang et al. 2015). Polymorphisms of the D2 dopamine receptor have been particularly implicated in patients with bipolar II, both with and without a comorbid anxiety state (Wang et al. 2014). Therefore, it is clear that specific polymorphisms relating to D1 and D2 receptors are linked with bipolar I and bipolar II, and thence are linked with increased suicidal risk.

## SUICIDE RISK

Many patients with bipolar disorder, even bipolar II, suffer suicidal thoughts (Rihmer 2007). It has long been documented that patients with bipolar spectrum disorders have increased lifetime rates of suicide compared with those with unipolar depression and other axis I disorders (Chen & Dilsaver 1996, Rihmer 2007). A 2005 study went on to demonstrate that patients with bipolar I and bipolar II were equally likely to experience suicidal ideation. It showed that patients with either of these mood disorders had an 80% chance of having either suicidal ideation or ideation with a suicide attempt at some point in their life (Valtonen et al. 2005).

## CONCLUSION

Given the role of dopamine in the pathogenesis of bipolar disorder, the rates of self harm and suicidal tendency in adolescents given diagnoses of unipolar depression together with the idea that many of these patients may be misdiagnosed and actually be presenting with a prodrome of bipolar disorder, it is certainly plausible that the use of SSRIs may not only be suboptimal in terms of symptom management but may be dangerously precipitating manic switch or the mixed state. We have demonstrated that the use of SSRIs in these patients may in fact be contributing to the increased risk of suicidal ideation. Therefore, whilst they present with a constellation of symptoms in keeping with unipolar depression, it appears that many are in fact developing bipolar disorder and are therefore, as a result of the significance of dopamine in the pathogenesis of bipolar disorder, being 'inadequately' treated with SSRIs.

Nonetheless, this should not necessarily translate to withholding antidepressant therapy in adolescents presenting with depressive episodes. As a consequence of the Black Box warning, a decreased use of antidepressants in the USA, Netherlands and Canada has been accompanied by a concurrent increase in suicide rates in adolescents (Gibbons et al. 2007, Katz et al. 2008). Furthermore, in a study by Isacson & Ahlner (2013), it was found that contrary to its intention, the Black Box Warning resulted in an increasing number of young depressives who did not receive antidepressants and the suicide mortality in this age group subsequently increased by 60% for five consecutive years (Isacson & Ahlner 2013). The individual analysis showed that this

increase occurred among young people who were not on antidepressant therapy.

In adolescents presenting with a depressive episode who may in fact be suffering from a prodrome of bipolar disorder, mistreatment with SSRIs might produce a suboptimal response or worse, increase suicidality. However, this alone is not sufficient to support a reduction in antidepressant therapy. Further research is needed in order to better distinguish these subsets of adolescents who later go on to develop bipolar disorder and thus guide appropriate treatment strategies.

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### Conflict of interest:

Mark Agius is a Member of an advisory board to Otsuka, Japan.

## References

1. Anderson RN & Smith BL: Deaths: leading causes for 2002: *Natl Vital Stat Rep* 2005; 53:1-89.
2. Baldessarini R, Faedda G & Hennen J: Risk of Mania With Antidepressants. *Arch Pediatr Adolesc Med* 2005; 159:298.
3. Chen Y & Dilsaver S: Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other axis I disorders. *Biological Psychiatry* 1996; 39:896-899.
4. Chilakamarri JK, Filkowski MM & Ghaemi SN: Misdiagnosis of bipolar disorder in children and adolescents: a comparison with ADHD and major depressive disorder. *Ann Clin Psychiatry* 2011; 23:25-9.
5. Cox GR, Callahan P, Churchill R, Hunot V, Merry SN, Parker AG & Hetrick SE: Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. *Cochrane Database Syst Rev* 2012; 11: Cd008324.
6. Cuellar AK, Johnson SL & Winters R: Distinctions between bipolar and unipolar depression. *Clin Psychol Rev* 2005; 25:307-39.
7. Duffy A, Alda M, Hajek T, Sherry SB & Grof P: Early stages in the development of bipolar disorder. *J Affect Disord* 2010; 121:127-35.
8. Forty L, Smith D, Jones L, Jones I, Caesar S, Cooper C, Fraser C, Gordon-Smith K, Hyde S, Farmer A, McGuffin P & Craddock N: Clinical differences between bipolar and unipolar depression. *Br J Psychiatry* 2008; 192:388-9.
9. Furukawa TA, Konno W, Morinobu S, Harai H, Kitamura T & Takahashi K: Course and outcome of depressive episodes: comparison between bipolar, unipolar and subthreshold depression. *Psychiatry Res* 2000; 96:211-20.
10. Gibbons RD, Brown CH, Hur K, Davis J & Mann JJ: Suicidal thoughts and behavior with antidepressant treatment: reanalysis of the randomized placebo-controlled studies of fluoxetine and venlafaxine. *Arch Gen Psychiatry* 2012; 69:580-7.
11. Gibbons R, Brown C, Hur K, Marcus S, Bhaumik D, Erkens J et al: Early Evidence on the Effects of Regulators' Suicidality Warnings on SSRI Prescriptions and Suicide in Children and Adolescents. *American Journal of Psychiatry* 2007; 164:1356-1363.

12. Goodwin FK & Jamison KR: *Manic-Depressive Illness* (2nd edn.). Oxford University Press, 2007.
13. Goodwin GM: Evidence-based guidelines for treating bipolar disorder: revised second edition-recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2009; 23:346-88.
14. Goodwin F & Jamison K: *Manic-depressive illness*. New York, NY. Oxford University Press, 2007.
15. Gould MS, King R, Greenwald S, Fisher P, Schwab-Stone M, Kramer R, Flisher AJ, Goodman S, Canino G & Shaffer D: Psychopathology associated with suicidal ideation and attempts among children and adolescents. *J Am Acad Child Adolesc Psychiatry* 1998; 37:915-23.
16. Hammad TA, Laughren T & Racoosin J: Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry* 2006; 63:332-9.
17. Harrison PJ: Molecular neurobiological clues to the pathogenesis of bipolar disorder. *Curr Opin Neurobiol* 2016; 36:1-6.
18. Hawton K, Casanas ICC, Haw C & Saunders K: Risk factors for suicide in individuals with depression: a systematic review. *J Affect Disord* 2013; 147:17-28.
19. Hetrick SE, McKenzie JE, Cox GR, Simmons MB & Merry SN: Newer generation antidepressants for depressive disorders in children and adolescents. *Cochrane Database Syst Rev* 2012; 11: Cd004851.
20. Huang CC, Lu RB, Yen CH, Yeh YW, Chou HW, Kuo SC, Chen CY, Chang CC, Chang HA, Ho PS, Liang CS, Cheng S, Shih MC & Huang SY: Dopamine transporter gene may be associated with bipolar disorder and its personality traits. *Eur Arch Psychiatry Clin Neurosci* 2015; 265:281-90.
21. Isacson G & Ahlner J: Antidepressants and the risk of suicide in young persons - prescription trends and toxicological analyses. *Acta Psychiatr Scand* 2014; 129:296-302.
22. Jane Costello E, Erkanli A & Angold A: Is there an epidemic of child or adolescent depression? *J Child Psychol Psychiatry* 2006; 47:1263-71.
23. Katz LY, Kozyrskyj AL, Prior HJ, et al: Effect of regulatory warnings on antidepressant prescription rates, use of health services and outcomes among children, adolescents and young adults. *CMAJ* 2008; 178:1005-1011.
24. Kato T: Molecular neurobiology of bipolar disorder: a disease of 'mood-stabilizing neurons'? *Trends Neurosci* 2008; 31:495-503.
25. Kesić M, Štefulj J, Mokrović G & Čičin-Šain L: The effect of chronic fluoxetine administration on anxiety-like behavior and expression of 5-HT-related proteins in rats with constitutively altered 5-HT homeostasis. *BMC Pharmacol Toxicol* 2012; 13:A30.
26. Kochman F, Hantouche E, Ferrari P, Lancrenon S, Bayart D & Akiskal H: Cyclothymic temperament as a prospective predictor of bipolarity and suicidality in children and adolescents with major depressive disorder. *Journal of Affective Disorders* 2005; 85:181-189.
27. Maletic V & Raison V: Integrated neurobiology of bipolar disorder. *Front Psychiatry* 2014; 5:98.
28. Nasrallah HA: Consequences of misdiagnosis: inaccurate treatment and poor patient outcomes in bipolar disorder. *J Clin Psychiatry*. 2015; 76:e1328.
29. Rihmer Z & Gonda X: Pharmacological prevention of suicide in patients with major mood disorders. *Neuroscience & Biobehavioral Reviews* 2013; 37:2398-2403.
30. Rihmer Z: Suicide risk in mood disorders. *Curr Opin Psychiatry* 2007; 20:17-22.
31. Rihmer Z & Gonda X: Antidepressant-resistant depression and antidepressant-associated suicidal behaviour: the role of underlying bipolarity. *Depress Res Treat* 2011; 2011:906462.
32. Severino G, Congiu D, Serreli C, De Lisa R, Chillotti C, Del Zompo M & Piccardi MP: A48G polymorphism in the D1 receptor gene associated with bipolar I disorder. *Am J Med Genet B Neuropsychiatr Genet* 2005; 134b:37-8.
33. Smith DJ, Griffiths E, Kelly M, Hood K, Craddock N & Simpson SA: Unrecognised bipolar disorder in primary care patients with depression. *Br J Psychiatry* 2011; 199:49-56.
34. Torack RM & Morris JC: The association of ventral tegmental area histopathology with adult dementia. *Arch Neurol* 1988; 45:497-501.
35. Usala T, Clavenna A, Zuddas A & Bonati M: Randomised controlled trials of selective serotonin reuptake inhibitors in treating depression in children and adolescents: a systematic review and meta-analysis. *Eur Neuropsychopharmacol*. 2008; 18:62-73.
36. Valtonen H, Suominen K, Mantere O, Leppamaki S, Arvilommi P & Isometsa ET: Suicidal ideation and attempts in bipolar I and II disorders. *J Clin Psychiatry* 2005; 66:1456-62.
37. Wang YS, Lee SY, Chen SL, Chang YH, Wang TY, Lin SH, Wang CL, Huang SY, Lee IH, Chen PS, Yang YK & Lu RB: Role of DRD2 and ALDH2 genes in bipolar II disorder with and without comorbid anxiety disorder. *Eur Psychiatry* 2014; 29:142-8.
38. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A & Boddington E: Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* 2004; 363:1341-5.
39. Wohlfarth TD, van Zwieten BJ, Lekkerkerker FJ, Gispen-de Wied CC, Ruis JR, Elferink AJ & Storosum JG: Antidepressants use in children and adolescents and the risk of suicide. *Eur Neuropsychopharmacol* 2006; 16:79-83.
40. Yao J, Pan Y, Ding M, Pang H & Wang B: Meta-analysis shows dopamine receptor D1 gene polymorphism is associated with bipolar disorder but not with schizophrenia. *Psychiatry Res* 2013; 210:1324-5.
41. Zisook S, Trivedi MH, Warden D, Lebowitz B, Thase ME, Stewart JW, Moutier C, Fava M, Wisniewski SR, Luther J & Rush AJ: 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.

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