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LETTER TO THE EDITOR

SSRIs-Related Behavioural Syndromes in Children and Adolescents

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Dear Editor:

Selective Serotonin Reuptake Inhibitors (SSRIs) have become increasingly the mainstay of treatment for a wide array of *depressive* and *anxiety* disorders in Child and Adolescent Psychiatry (CAP) reflecting *efficacy* coupled with reasonable *safety* and tolerability- unlike its predecessors; tricyclic antidepressants (TCAs). Dire shortage of clinicians trained in Child and Adolescent psychotherapy renders SSRIs a default first-line treatment. FDA-approved SSRIs in CAP are sertraline, fluvoxamine, fluoxetine, and, escitalopram. Apart from expected *somatic* side-effect profile of SSRIs related to excess serotonin in the synaptic cleft stimulating post-synaptic 5HT2A, 5HT2c, and 5HT3 receptors, *behavioural* syndromes are now more frequently encountered in clinical practice that mandate special characterization.

Here, I delineate *eight* of these syndromes- mostly based on clinical experience, as there is dearth of pertinent data in literature notably regarding CAP. Its neurobiologic correlates are yet to be defined.

1. ***SSRI-Activation Syndrome*** (Reinblatt, dosReis, Walkup, & Riddle, 2009):

- It is more in CAP populations;
- It is commonplace;
- Tends to occur early-on during course of treatment;
- Mostly manifests as agitation, dysphoria or akathisia, but with no striking mood changes;
- It is not indicative of latent bipolarity;
- And responds to dose reduction or slower titration.

2. ***SSRI-Manic/Hypomanic Switch*** (Joseph, Youngstrom, & Soares, 2009):

- It is less common than the activation syndrome;
- It is usually of later onset;
- Manifests striking mood changes, with hyperactivity;
- Might continue symptomatic after stopping SSRI;
- And indicative of bipolar (III) disorder;
- Cycle acceleration is also possible;
- Stopping culprit agent is mandatory or cautious use under umbrella of mood-stabilization.

3. ***SSRI-Discontinuation Syndrome*** (Hosenbocus, & Chahal, 2011):

- It occurs with prolonged use (at least 1 month);
- Follows abrupt cessation;
- It takes place within 1-7 days of stopping of offending agent;
- Notably manifest when higher doses employed;
- More likely with short half-life agents;
- It presents in form of dizziness, insomnia, electric shock-like sensations, nightmares, flu-like symptoms;
- Paroxetine is notorious in this regard;
- Gradual tapering, benzodiazepine coverage or switch to fluoxetine is all helpful avoiding stopping it "cold turkey".

4. ***SSRI-Emotional Blunting*** (Reinblatt, & Riddle, 2006):

- It shows as apathy or indifference;
- Might be related to resultant secondary dopamine deficiency with boosting 5-HT tone;

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- Frontal lobe dysfunction has been postulated;
- It is of insidious onset;
- Seems to be dose-dependent (evident at high doses);
- Agents boosting DA drive are helpful e.g. stimulants or bupropion.

5. ***SSRI-Unmasking Comorbidities:***

- It has been shown that effectively treating anxiety might reveal underling disruptive disorders or ADHD;
- Conversely, anxiety/depression can masquerade as "counterfeit ADHD";
- It warrants treatment accordingly, with prioritized sequential approach based heavily on severity of symptomatology.

6. ***Serotonin Syndrome*** (Kant, & Liebelt, 2012)***:***

- It is likely especially if combined with other serotonergic agents or in the setting of overdosing;
- Manifests as altered mental status (AMS), fever, gastro-intestinal (GIT) symptoms, hyperkinesias;
- 5-HT2 antagonists e.g. cyprhepatidine, α -2 agonist; dexmedetomidine, and supportive measures are the mainstay of treatment, besides stopping the offending agent.

7. ***SSRI-related Suicidality:***

- Activation of suicidal ideations- paradoxical suicide is noted where mood symptoms improvement lag behind regaining of energy levels;
- FDA black box for those below 25 years- in 2004, based on data from 23 trials comprising 4300 patients, FDA issued this black-box warning of increased risk of suicidal thinking, feeling, and behaviour associated with antidepressants use in young population (Naguy, 2016);
- 2-fold increase compared to placebo; (4% vs. 2% respectively);
- And more when it is used for depressive than for anxiety or OCD disorders;
- Still, benefit of use clearly outweighs this theoretical risk as demonstrated by American College of Neuropsychopharmacology (Mann et al. 2006);
- AACAP developed practice parameters as regards frequency of close monitoring when intiating SSRIs in the first 12 weeks.

8. ***SSRI-Withdrawal Mania/hypomania*** (Goldstein et al., 1999):

- It is self-limited, paradoxical phenomenon;
- Has been reported in mood disorders (uni or bipolar);
- Might be related to nor-adrenergic (NE) overactivity and overriding cholinergic tone.

This list is not all-inclusive. It is ever-expanding as clinical data accrues. It merely sheds some light on oft-times under-recognized SSRIs behavioural syndromes. It beehoves clinicians be vigilant and mindful of these syndromes that might be a source of diagnostic confusion with syndromic relapse/recurrence and inform subsequent treatment directions accordingly. Hence, there is a pressing need to dissect the neurobiology of these syndromes and better define them as clinical entities

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