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Treatment of Depression in Smokers: An Emerging Frontier of Personalized Medicine

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Introduction

Depression affects people of all ages, races and social classes around the world. It was predicted to be the second largest contributor to the global disease burden and total mortality by 2020. In India, the average prevalence of depression is 5.25% among persons aged 18 years and above. The current prevalence is 2.68%, reflecting that 01 out of 20 Indians has suffered from depression in the past.

The correlation between serum/plasma concentrations of antidepressants and their clinical response is not well delineated. However, sub-therapeutic serum concentrations are known to undermine clinical response.

Most antidepressants, including sertraline, are metabolized by cytochrome P_{450} hepatic microsomal enzyme system. The activity of this enzyme system differs among individuals leading to varying serum levels among those receiving the same dose. Smoking is an important variable that induces isoenzymes and hence smokers may achieve reduced serum concentration of antidepressants as compared to non smokers. There is evidence of reduction in serum concentrations of fluvoxamine, duloxetine, trazodone and mirtazapine in smokers. However, there is scant data regarding the clinical impact of such reduction. Furthermore, data regarding impact of smoking on pharmacokinetics of some commonly used drug such as sertraline and citalopram is inconclusive.

The prevalence of smoking in India is 24% in males and 2.7% in females. Around 40-50% of patients of depression smoke regularly. The association between depression and smoking is complex and inconsistent as highlighted in 2017 by Fluharty, et al. Some studies suggest an association between smoking and mental health and that smoking increases with severity of disease. However, the cause and effect relationship is not clear. Effect of smoking on treatment of schizophrenia is known where in smokers are known to require more neuroleptic dose. Similar association between smoking and treatment of depression is not clear 9-11 the relationship between no of cigarettes smoked and quantum of enzyme induction also is not clear. Though there is a general agreement that heavier smokers will have more enzyme induction, the linearity or otherwise of the relationship with cut off points, if any, has not been ascertained. Also, it is difficult and imprecise to classify smokers into various categories due to factors like recall bias and underreporting of smoking quantum. Hence most of the studies use a binary classification of smokers and non smokers. CDC definition of 'current everyday smoker an adult who has smoked at least 100 cigarettes in his or her lifetime, and who now smokes every day', is the most frequently used one.

Description

Despite having relatively better safety profile and clinical effectiveness, SSRIs are known for their adverse effect on body weight 11,12,13 risk of type 2 diabetes mellitus 14,15 association with dyslipidemia 14,16,17 and male sexual function. Depression, also, is associated with weight gain and increased waist circumference 18,19 dyslipidemia 20,21,22 and type 2 DM. 11,23 however, data regarding association of depression and SSRIs with above mentioned conditions is not uniform.

Smoking also increases the risk of developing metabolic syndrome *via* the development of central obesity and insulin resistance. Dyslipidemia and smoking are major risk factors for a number of cardiovascular disorders *viz*. coronary artery disease and cerebrovascular disease esp in Indian population, where there is a rising trend of cardio-metabolic diseases. So we have an illness (depression) and its treatment (SSRIs) both having similar metabolic fallouts, a relationship.

Which is further complicated with a confounder *i.e.* smoking. What further complicates the issue is the fact that interse relation between all these three variables is not linear and objective.

The aforesaid leads us to three important questions *viz*. Do smokers tend to achieve reduced serum levels, do they respond differently to similar serum levels and whether use of SSRIs will negatively impact the cardio metabolic profile of the patient.

Mohan, et al. have treid to partially address the first two questions through their observational study. They have reported that smokers responded poorly to treatment of depression to sertraline. Quantitative fall in HAMD scores was more in non smokers as compared to smokers which was similar to the fall in HAMD score seen in other studies. They have also derived that NNH for risk of not

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having remission after 08 weeks of therapy is 4, with smoking as the variable/intervention. In other words, for every 04 depressed individuals who smoke, one extra individual is not likely to have remission after 08 weeks of therapy with sertraline, *vis*. a non smoker. Any NNT/NNH of less than 10 is considered to be 'good enough' and is likely to be clinically relevant in day to day clinical practice.

Conclusion

They also observed a poor correlation between serum sertraline levels and clinical response (fall in HAMD score) among the entire study cohort. These results are in consonance with available literature, as no SSRI has demonstrated a clear concentration-clinical effect relationship. 39, 40 Further, since serum sertraline levels were similar in both the groups, the difference in clinical response is not explained by pharmacokinetics. Thus, they have conclude that the pharmacodynamics of sertraline is different in smokers as compared to non-smokers.

More such studies (preferably longer term) involving other antidepressants are required to further address this question. Including cases of severe depression, including both genders and stratification of smokers as per numbers of cigarettes smoked will lend more weight to the results.

As regards the cardio metabolic fall out of SSRIs, various studies have concluded that SSRIs are associated with increase in LDLc and triglyceride levels. Evidence regarding the effect of SSRIs on HbA1C and fasting plasma glucose is equivocal. Wie F, et al. in their study have further concluded that increased LDL levels due to paroxetine and sertraline use can be ameliorated with use of lipid medication.

The aforementioned opens up some interesting questions. In Indian population, is this metabolic fallout of SSRIS serious enough so as to preclude their use in this population, should they be co prescribed with statins only, should their use be precede by lipid profiling of the patient.

The effect of smoking on pharmacokinetics and pharmacodynamics of SSRIs and metabolic effects of SSRIs are important aspects to consider before prescribing SSRIs. Till such time more evidence is generated, smokers may require careful dose calibration and rigorous monitoring.

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