Reviewer’s report

Title: Amphetamine-induced psychosis - a separate diagnostic entity or primary psychosis triggered in the vulnerable?

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Reviewer: R. Andrew A Chambers

Reviewer’s report:

In this review focusing on the comparison (and/or relationship) between psychostimulant-induced psychoses and endogenous psychotic disorders (e.g. schizophreniform disorder), the authors provide a clearly written update and summary of available clinical data. The paper references many papers that should be considered as core reading for trainees in psychiatry and psychopharmacology, (and will itself represent such a reference) and will provide investigators with a handy citation resource for their own manuscripts and grants pertaining to this area of research. The authors succinctly and convincingly utilize their literature review in proposing that categorization frameworks that try to make diagnostic distinctions between pharmacologic vs. endogenous psychosis (e.g. clinical attempts to frame patients as having one or the other) are probably quite artificial because these conditions probably really occur as co-occurring processes where the liability to one form of psychosis lends itself to the other. Adapting the stress diathesis model of mental disorders to this perspective, the authors provide a more compelling view of acute psychoses as representing the culmination of many overlapping/interacting dynamics. We suggest only a few changes or additions in content and form to improve the strength of the manuscript (all as minor essential revisions):

1. The authors focus on psychostimulants (i.e. cocaine and amphetamine), but there is growing evidence that the same dynamics they describe also apply to cannabis (e.g. see studies by D. Cyril. D’Souza et al, where THC was delivered to healthy volunteers and people with schizophrenia). Although dealing with cannabinoids in a major way is beyond the scope of this report, isn’t it worth mentioning that what the authors are describing with respect to stimulants is clearly not isolated to stimulants only and so probably cannot be attributed specifically or exclusively to the mechanisms of actions that stimulants are most closely associated with (e.g. dopamine).

2. The authors are focused on how vulnerability to psychosis on stimulants is probably a product of dose history and underlying brain vulnerability to psychotic reactions in general (e.g. genetics of schizophrenia or other psychotic mental disorders). It might be useful in this review (and in fact would further buttress their central thesis) to also at least briefly mention and provide some evidence in support of the converse dynamic that may also be in play, that having an underlying psychotic disorder makes one more vulnerable to compulsive use of psychostimulants.
3. The review is fairly complete from a clinical-data -human subjects standpoint but does not mention animal modeling data that actually is very much in support of the perspective they are advancing, and may be suggestive of underlying mechanisms in play beyond the DA system. For instance, in our own work (Chambers et al. Biol Psy 2004 & 2010, Psychopharm, 2010) we have observed that a neurodevelopmental animal model of schizophrenia(not itself caused by stimulant exposure) potentiates not only the acute effects of psychostimulants, but elevates long lasting psychostimulant-induced behavioral sensitization curves resulting from chronic dosing. In this modeling, the core neural mechanisms in play seem to more directly involve abnormalities in the way cortical-striatal networks (that primarily use GLU and GABA neurotransmission) read DA signaling (downstream from the DA synapse) rather than abnormalities in DA transmission per se. Even beyond our own work in this area, other labs have also demonstrated similar interactive dynamics (as the authors describe) between other animal models of psychosis and other non-stimulant psychoactive drugs (e.g. like PCP).

4. Minor corrections:

ABSTRACT
A) On page 2 in the first line, the word “populations” should be singular.
B) On the same page, “common to both conditions” should be written instead of “common for both conditions”.

INTRODUCTION
C) On page 3 in the first line, “decreasing fatigue” should be corrected to “decrease fatigue”.

RISK FACTORS AND ACUTE VS, CHRONIC PSYCHOSIS
D) On page 7, the word “figures” is misspelled as “figurs”.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.
Kalyan Rao, MD.

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R. Andrew Chambers, MD