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Can psychedelics be the treatment for the crisis in psychopharmacology?

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1. Introduction

For the past few years, we have been witnessing a crisis in the field of psychopharmacology. Generally, it takes a decade and up to a billion dollars in investment to get a drug on the market. Furthermore, the majority of new drugs are ruled out during the pre-clinical phase. Less than 20% of the selected drugs make it to Phase-III evaluation involving humans. Drug development has never been an easy task. However, in psychiatric drug research there are additional difficulties that have led to the current crisis.

Tracing the history of psychiatric drug research helps map out the crisis that this field is currently facing. Before 1950s, only barbiturates and chloral hydrate were available for the treatment of psychiatric symptoms. These drugs were ineffective and were associated with serious adverse effects. But in the 1950s and early 1960s, several novel drug classes were discovered for the treatment of psychiatric disorders, a process that has been referred to as the "psychopharmacology revolution".[1] With more effective and safer drugs, the field of psychiatry developed new patterns of assistance, reducing the number of patients admitted to institutions and therefore improving their quality of life. The biomedical model that was developed based on these observations has been extensively criticized.[2,3] Some authors suggest that this model has produced the current conceptual crisis in psychiatry,[4] generating potentially erroneous situations such as excessive confidence in oversimplified treatments, including those based only on pharmacotherapy (or, worse, polypharmacy)[5].

Additionally, early psychopharmacological research faced various limitations, as Horrobin[6] explained in detail in an interesting text published in the *Oxford Textbook of Medicine*. He found that the five most successful therapeutic strategies to be used in the modern history of psychiatry were drugs developed (or rediscovered) during the 1950s or after: lithium, monoamine oxidase inhibitors, phenothiazines, tricyclic antidepressants, and benzodiazepines. The first three drugs listed were discovered by serendipity, and the final two were discovered through discredited screening techniques. Horrobin[6] subsequently concluded that these discoveries were not dependent on the regular medical research strategy.

These and other issues mentioned by Horrobin more than 30 years ago were recently highlighted anew by Insel and Sahakian,[7] as well as in statements from various eminent health professionals, suggesting that the state of psychopharmacology research has not changed significantly in the past few decades. Both DePaulo,[8] past chairman of the Department of Psychiatry and Behavioral Sciences at Johns Hopkins University, and

Insel,[9] former Director of the National Institute of Mental Health, have noted that modern psychopharmacological treatments are not more beneficial than past ones, despite their higher cost. In addition, Fibiger,[10] former Vice President of Neuroscience at Eli Lilly, has stated straightforwardly that psychopharmacology is in crisis. This is evidenced by the reality that not one innovative drug has reached the psychiatric market in more than 30 years. This is partly due to widely-used yet questionable practices, such as making minimal modifications to drugs that are already available and commercializing them as "new" products (known as "me-too" drugs). For this reason, our present psychiatric drugs are little better than those that were available in the 1950s.[9,11] One of the constraints hampering drug development may be the fact that the molecular targets of psychiatric drugs have not changed in the last 50 years, and even today we do not understand some of the mechanisms through which they work.[12] This lack of knowledge about the exact mechanisms is worsened by an inability to validate the fundamental hypotheses about mental disorders.[13]

Evidently, we are lacking innovative approaches, and we need to use creative and efficient strategies in order to improve our understanding of psychiatric drugs and their effects. Focusing on certain molecular targets exclusively would be a limited approach, at least if it is not combined with psychotherapy. Furthermore, chronic treatment with these medications might be more harmful than beneficial.[14,15] This is evident in the case of benzodiazepines, one of the most widely-used classes of drugs.[16] Based on the above, it can be deduced that psychiatry is facing serious challenges, since psychopharmacology (which offers the best therapeutic strategies in this regard) is in crisis. Furthermore, this crisis is having an inescapable negative impact on public health.[17]

2. Examples of the crisis

We can think of depression and post-traumatic stress disorder (PTSD) as examples of conditions impacted by this crisis. Many meta-analyses suggest that drug-placebo differences are minimal in antidepressant treatment[18–20] and that antidepressant drug treatments are useful only in cases of severe depression.[21,22] In addition to their questionable efficacy, antidepressants can produce serious adverse reactions.[23–25]

The pharmacological treatment of PTSD is also in crisis, as the PTSD Psychopharmacology Working Group of the US Department of Veteran Affairs recently stated.[26] The prevalence of lifetime PTSD among the general population is approximately 6.8%.[27] Despite this high prevalence, there are only two medications approved for the treatment of PTSD, sertraline and paroxetine, which only produce reduction in symptom severity rather than remission of PTSD.[26] The fact that antidepressants cannot produce remission of PTSD symptomatology may be because PTSD is not an aberrant response of the brain, but a normal response to an aberrant situation. This is why patients with PTSD tend to respond better to psychosocial

treatments than to pharmacotherapy.[28] Since 2001, no new medication has been approved for the treatment of PTSD, despite the significant need. This scenario has pushed clinicians to adopt poly-pharmacological approaches for the vast majority of their patients, using off-label medications regarding which there is little empirical guidance concerning risks or benefits.[26] Among these medications, we find benzodiazepines, which are not only ineffective but are also associated with negative psychotherapy outcomes, aggression, depression, and illicit substance use in PTSD patients.[29]

While the situation is especially troubling in terms of depression and PTSD, the psychiatric drugs crisis is widespread. In 2011, an editorial published in the *British Journal of Clinical Pharmacology* claimed that in one year they only published five papers concerning CNS drugs, none of which involved novel drugs.[30] They also expressed concerns over the cessation of psychiatric drug research as conducted by GSK, Astra Zeneca, and other major pharmaceutical companies. Andrew Witty, CEO at GlaxoSmithKline, alleged that it is not possible to test the efficacy of psychiatric drugs even after large-scale trials.[31]

3. Psychedelic drugs as treatment for the crisis

Recently, the Royal Society convened an International Scientific Seminar in order to discover innovative solutions to the psychiatric drugs crisis. One of the conclusions reached was that we need a paradigm shift in terms of how we view and approach mental health research.[31] Similar conclusions were drawn in a report published by Nesta[32] that focused on the *biomedical bubble* in which life sciences are immersed. Some researchers pointed out recently that psychedelic-assisted psychotherapy might offer a partial solution for overcoming this crisis.[33,34] Treatment targets for disorders like depression and PTSD have been too focused on symptom relief instead of recovery.[35,36] Psychiatric disorders are complex, so instead of an oversimplified neurobiological approach, a more integrative treatment is required that combines pharmacological tools with psychosocial interventions.[31] Psychedelic-assisted psychotherapy could satisfy this need, offering pharmacological action along with enhanced psychotherapeutic interventions.[33]

Psychedelic drugs activate different G-protein-coupled receptors (GPCRs), but several studies identified 5-HT2A as the main receptor responsible for the behavioral effects of psychedelic drugs.[36] Although serotonin acting via 5-HT2 receptors produces pro-inflammatory actions,[37] psychedelic drugs such as lysergic acid diethylamide (LSD) or 2,5-Dimethoxy-4-iodoamphetamine (DOI) primarily show potent anti-inflammatory effects.[38] The activation of 2A receptors has also been associated with neurogenesis[39,40] and neuronal plasticity.[41] Remarkably, N,N-Dimethyltryptamine (DMT) and other psychedelics have been termed “psychoplastogens” due to their promotion of rapid structural and functional neural plasticity.[42] This emphasis on the modulation of neural

circuits through fast-acting psychoplastogens instead of rectifying chemical imbalances using long-term treatments suggests a considerable paradigm shift. DMT and LSD also activate trace amine-associated receptors (TAARs),[43] a GPCR subfamily the agonism of which is associated with antipsychotic, antidepressant, and antiaddictive properties.[43] For a complete review of the pharmacological mechanisms of psychedelic drugs, see Kyzar et al. 2017.[36]

Regarding the enhancement of psychotherapeutic interventions, psychedelic drugs could trigger meaningful personal concerns,[44,45] facilitate introspective insights[33] and enhance the relationship between the therapist and the patient,[46] among other effects. Additionally, there are some idiosyncrasies of this kind of assisted psychotherapy that deserve mention. First, the drug (generally psilocybin, LSD or ayahuasca) is used on one or a few occasions during psychotherapy sessions in order to overcome obstacles and to catalyse the therapeutic experience.[33] Second, it is assumed that the psychedelic experience itself, and not only the pharmacological effect, will offer therapeutic effects.[47].

In the last 15 years, interest in the therapeutic potential of psychedelic drugs has increased. Several clinical trials have been published and show promising results for the treatment of depression,[48–51] anxiety in cancer patients,[55–55] addictions,[56] social anxiety in autism,[57] and PTSD.[58–62] See Table 1. Actually, beyond the mere demonstration of efficacy, it has been suggested that some of these treatments could represent the first evidence-based and pharmacologically-mediated cure in psychiatry.[63] For a review of the clinical use of psychedelic drugs, see dos Santos et al. 2016.[64] In addition to these substances, it is also remarkable the therapeutic potential that ibogaine has shown for the treatment of addictions, mostly in the treatment of opioid dependence,[65] becoming a potential solution for the opioid crisis occurring in many countries. The first RCT in which ibogaine will be administered in patients with alcoholism will begin in 2019 (ClinicalTrials.gov Identifier: NCT03380728). In contrast with clinical trials, the notion that psychedelic drugs are harmful is challenged when we examine real-world situations. Psychedelic drug use is associated with a lower rate of mental health problems[66] and with reduced psychological distress and suicidality[67] in population studies.

RCT	Core topic	Nº of patients	Main findings	Limitations
Grob et al. 2011	Psilocybin for the treatment of anxiety associated with life-threatening disease	12	Significant reductions in anxiety after 1 and 3 months post-treatment	No control group
Mithoefer et al. 2011	MDMA for the treatment of PTSD	20	MDMA-assisted psychotherapy can be safely administered to PTSD patients, and it may be useful in patients refractory to other treatments	Potential selection bias Per-protocol analysis
Oehen et al. 2013	MDMA for the treatment of PTSD	12	MDMA-assisted psychotherapy can be safely administered in a clinical setting	Unbalanced groups Low adherence to MDMA-psychotherapy protocol
Gasser et al. 2014	LSD for the treatment of anxiety associated with life-threatening disease	12	When administered safely in a medically supervised psychotherapeutic setting, LSD can reduce anxiety	Potential selection bias
Griffiths et al. 2016	Psilocybin for the treatment of anxiety associated with life-threatening disease	51	Immediate and long-term decrease of anxiety after administration of high-dose psilocybin	Measures not validated Low external validity
Ross et al. 2016	Psilocybin for the treatment of anxiety associated with life-threatening disease	29	Immediate and sustained improvement of anxiety and depression	Potential selection bias
Danforth et al. 2018	MDMA for the treatment of social fear and avoidance in autistic adults	12	MDMA- assisted psychotherapy can be safely administered and produce rapid and durable improvement in social anxiety symptoms in autistic adults	AEs reported Inclusion criteria not comprehensive
Palhano-Fontes et al. 2018	Ayahuasca for the treatment of depression	29	Ayahuasca is safe and dosed within an appropriate setting, has therapeutic value to treat depression	No follow-up
Ot'alora et al. 2018	MDMA for the treatment of PTSD	28	PTSD symptoms remained lower than baseline at 12-month follow-up with 76% of the patients not meeting PTSD criteria	Limited generalizability of findings. No control group to compare at follow-ups

Table 1. Modern Randomized Clinical Trials (RCT) involving the administration of psychedelic substances. RCT= Randomized Clinical Trial; MDMA= 3,4-Methyl

enedioxymethamphetamine; PTSD= Posttraumatic Stress Disorder; LSD= Lysergic acid diethylamide; AEs= Adverse Events.

The *Journal of Psychopharmacology*, *Psychopharmacology*, and *Neuropharmacology* dedicated entire issues to psychedelic drugs, in December of 2016, February of 2018, and November of 2018, respectively. The United States' Food and Drug Administration has designated MDMA and psilocybin-assisted psychotherapies as "breakthrough therapies", and Phase-III and Phase-II clinical trials are in development for these drugs, respectively. So, it is quite probable that psychedelic-assisted psychotherapy will be approved for the treatment of some disorders in the next few years.

Preliminary evidence from a public health approach[68] showed that a long-term ritualistic use of psychedelic drugs is associated with higher positive perception of health or with a healthy lifestyle. Additionally, 56% of the sample could diminish the use of prescription drugs due to their use of psychedelic drugs. This finding encourages us to continue researching the usefulness of psychedelics as a means to overcome at least part of the crisis in psychopharmacology. Apart from clinical approach, we should remember that there is a growing tendency towards the ritualistic and communal use of plants like ayahuasca, which can function as both a health and a self-care practice.[69] These plants have been traditionally used in many cultures, and must be framed as such within the pluralistic medical systems.[69] The use of these plants by shamans, traditional healers or by religious/neo-shamanic communities, alongside with biomedical research and clinical applications, must be concurrently respected and permitted.

The experiences induced by psychedelic drugs in therapeutic contexts seem to change an individual's personality structure into a healthier one,[70] and they have been related to pro-environmental behavior[71] and lower intimate partner violence levels.[72] So, we can also expect the associated social and community benefits that psychedelic-assisted psychotherapy and traditional ceremonies offer. Most importantly, however, it is hoped that patients' satisfaction with their treatment will increase, as current patient satisfaction regarding antidepressant drug treatment remains low.[73]

Despite all of the advantages above mentioned, we must not forget the limitations of psychedelic-assisted psychotherapy. Current evidence is limited, so more studies are needed in order to better describe potential serious adverse events and the effectiveness of this treatment. Additionally, not all patients would be candidates for this treatment. For instance, it should not be used in patients with personal or family history of nonpsychotic mania or any psychotic illness, since psychotic episodes can appear.[74] Additionally, some cases were published showing that subjects without the previous characteristics also developed psychopathological crises, but the incidence of these situations appears to be rare.[74] For this reason, patients who will be administered with psychedelic drugs should be upon proper screenings and strict inclusion / exclusion criteria.[75]

4. Conclusion

The paradigm shift that psychopharmacology now arguably requires could be accomplished in part by the greater introduction of psychedelic therapies. They represent an innovative approach in mental health, with the use of safer drugs that can be combined with enhanced psychotherapeutic interventions. Furthermore, in terms of use, only a few administrations are necessary, so this could mean a savings of millions of dollars for public health systems in both direct and indirect costs, ranging from the direct health costs of current treatments to the price paid by patients and families that find themselves impaired by mental illness and unable to work or cope.

Author contributions

G.O. and J.C.B. contributed equally to this work.

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