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‘Psychedelics and psychopathology’

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Prof. Dr. Leon Kenemans (Head of Department, Experimental Psychology) analyses the use of psychedelic compounds in the treatment of psychiatric disorders, outlining their safety, efficacy and potential future as therapeutic medicines.

It is sometimes asserted that recent clinical trials have shown promising results in the treatment of psychiatric disorders. But how promising are these results? The answer to this question depends on the definition of a promising result. For some researchers, a desired therapeutic effect in an open-label study may be promising. In such a setup there is no (placebo-) control group, so any therapeutic effect may be due to other factors such as placebo. The promise then is that the effect will also surface in a subsequent randomized placebo-control trial (RCT), with a sufficiently large sample size (which could be considered as a phase-2 trial). For others, only a desired therapeutic effect found in exactly such a phase-2 trial would count as promising. In that case, the real proof of the pudding must come from subsequent phase-3 trials: multi-site combined phase-2 trials, compounding samples from different subpopulations (for a given diagnosis), to find out about replicability and generalizability across these different subpopulations, which may differ in clinical background and ethnicity, social-economic status and so on, but also etiologically.

Here are some specific examples. The application of MDMA in the treatment of anxiety disorders, especially PTSD, is at a phase-2-phase-3 transition stage. A number of successful phase-2 trials (summarized in Mithoefer et al., 2019) have been reported, conducted by mainly the same research group, and invariably using MDMA as an adjuvant for a rather specific form of psychotherapy. Recently, a first phase-3 study has been reported, with positive effects observed from 15 sites in patients from three countries (USA 77; Canada 9; Israel 5) (Mitchell et al., 2021). On the other hand, the application of psilocybin for depression and/or anxiety is probably more in an open-label-phase-2 transition, as RCTs have so far been published only for subgroups of cancer patients (Goldberg et al., 2020). A third more or less celebrated application, ketamine for depression, has also seen a number of successful phase-2 trials (e.g., Canuso et al., 2019; Daly et al., 2019; Reinstatler & Youssef, 2015). By now, two full-blown phase-3 studies have been published, one finding a significant improvement as a result of ketamine plus a more standard antidepressant over placebo plus this same standard antidepressant (Popova et al., 2019), whereas another one found no significant effect (Fedgchin et al., 2019). Two other phase-3 studies have so far been published only as conference proceedings, which have usually not been subjected to rigorous peer-review procedures (Daly et al., 2019; Ochs-Ross et al., 2019).

So, when will psychedelics become a viable option for treating mental disorders? Somewhat oddly, ketamine has been approved in 2019 by the FDA as well as the EMA for treatment-resistant depression as a supplement to a regular antidepressant (Breeksema et al., 2020). Most researchers, clinicians, and policy makers would state that only after sufficient phase-3 evidence, a substance can be registered for clinical application. One may question whether all current standard medications have met this criterion, but that is certainly no reason to relax it with regard to new alternatives such as psychedelics. As explained above, phase-3 trials have all kinds of added value relative to phase-2 trials. To highlight one specifically: It has repeatedly been shown, especially during the last decade or so, that there is great interindividual variation in treatment response within a population with any certain diagnosis. Furthermore, this variability may manifest easily in inconsistencies between isolated phase-2 trials, hence the need for phase-3 trials. The awareness about interindividual variability is increasingly accompanied by the advocated need for precision or personalized psychiatry (Wu et al., 2020).

If psychedelics become a viable option, can they replace existing therapies such as SSRIs? All the above is part of the answer to this question, but there is more to it. Some further promising results suggest that psychedelics may at least supplement traditional interventions such as SSRIs, for at least two reasons. The first is that they may have immediate, acute positive effects. For example, open-label or phase-2 trials have reportedly revealed symptom-reducing effects within hours or at most a day after administration. This may potentially fill an important gap, as most traditional pharmaceutical interventions take one to several weeks of administration for a noticeable clinical effect. Note also that ketamine has

been FDA/EMA approved as a supplement to regular treatment, that is, to fill the gap. Secondly, it may be that these immediate short-term effects are complemented by desired longer-term effects, over the course of weeks, months, perhaps as much as years, even after only a limited amount of initial administration. If this bears out in studies with corresponding periods of observation, then psychedelics could not only supplement traditional pharmaceuticals but also replace them. However, as of yet, the true nature of such longer-term effects is mainly unexplored territory.

Another question is whether psychedelics are useful at all without (assisting) psychotherapy. For ketamine the answer seems to be yes, although perhaps not so much without assisting regular pharmacotherapy. Other psychedelics (including MDMA, psilocybin, but also cannabinoids) have been evaluated mainly, but not always, in combination with various kinds of psychotherapy. It is conceivable that especially psilocybin may also induce desired effects by itself, as the subjective effect of the drug may include a psychedelic experience that is instrumental in improving psychopathology by itself (probably much more than in the case of MDMA or ketamine); however, of two RCTs in cancer patients, one examined psilocybin in combination with psychotherapy (Ross et al., 2016), whereas the other did not (Griffiths et al., 2016). An alternative perspective is that psychedelics, or other non-traditional substances, are especially effective in enhancing learning processes that in turn facilitate the termination of pathological conditions. One example is D-cycloserine (DCS) and its application as adjuvant to exposure therapy in a variety of anxiety disorders, which produced beneficial effects in quite a number of initial studies (see Kenemans, 2020, p. 122). That is, DCS at least reduced the number of exposure-therapy sessions needed to achieve the desired clinical effect. Importantly, this apparent learning-promoting effect of DCS could be explained (or perhaps even predicted) from its known properties as an allosteric NMDA-agonist, the NMDA receptor being one of the most prominent receptors known to be involved in learning and memory. This is another aspect to consider: insight into the biochemical functional mechanism underlying the possible beneficial effect of a new substance not only facilitates its acceptance as a viable treatment option by the scientific community, but also offers possibilities to improve its efficacy, e.g. by identifying specific subpopulations of responders versus non-responders. A similar detailed neurobiological analysis has surged with respect to ketamine and the NMDA receptor (H. Wu et al., 2021).

So what does the future hold for psychedelic medicine and what needs to be done? The turn MDMA research has taken is probably the way to go, and will ultimately reveal how substantial the psychiatric application of ketamine, psilocybin, MDMA itself, and other psychedelic substances can be. But even for MDMA itself, a number of issues have to be resolved. These include whether the effects will stand in combination with other forms of psychotherapy and in the hands of other research groups, but also in (head to head) comparisons with other established therapies, in terms of both efficacy and cost-effectiveness.

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‘Cerebral organoids to model human brain development and neurological disorders’

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Grow your own brain, did you say? Werner Dykstra (PhD candidate at University Medical Center Utrecht Brain Center) provides a brief history of how pluripotent stem cells are used to produce 3D brain structures called Organoids and further discusses how they influence his work on Alexander Disease.

In 2008, Shinji Yamanaka and his group made an astonishing discovery. If you would take skin cells and put some factors (thereafter catchingly referred to as Yamanaka factors) on them, they would miraculously transform into stem-like cells (Takahashi et al., 2007; Takahashi & Yamanaka, 2006). This was a massive breakthrough, because stem cells have the potential to virtually become any other cell type, allowing us to bypass the barrier of actually having to take cells from people’s organs for research. This is especially challenging when it comes to the brain and the very procedure of doing so could actually inflict more damage to the person’s brain than the benefits of research would reap. Dr. Yamanaka would call these cells “induced pluripotent stem cells”, or iPSCs for short. “Induced”, because they were not always like that and he induced them to be that way (with his factors). “Pluripotent”, because they have the potential to acquire multiple faiths, meaning they can become any kind of other cell. And finally, “stem cells”, because they have stem cell-like properties, which again mostly refers to the fact that they can become any kind of other cell. Another brilliant aspect of these iPSCs is that they have the same genetic make-up as the skin cells from which they were derived, including some (possibly) disease causing mutations. As if this discovery were not brilliant enough, Madeline Lancaster, in the lab of Jürgen Knoblich, building on the work of Yoshiki Sasai who pioneered the very first 3D brain-like structures, published the first article on brain, or cerebral, organoids (Lancaster et al., 2013). They discovered that when you grow these iPSCs in 3D, that is, you cluster them in the center of a cell-culture plate and do not allow them to attach to the plate, these balls of iPSCs called embryoid bodies (probably called embryoid, because they are reminiscent of the very early stages of development when humans are nothing but a ball of pluripotent cells, and probably called bodies, because that’s what they are) could then be allowed to acquire features of early human brain development, simply by removing the factors that keep the cells of the embryoid bodies in the stem cell like state (Figure 1).

What was most remarkable about this transition from pluripotency to actual brain development was that the embryoid bodies independently knew how to form certain brain structures.

Apparently, the information on how to build a brain, which is arguably the most complex object that nature has developed, actually exists somewhere in those cells. Scientists quickly discovered that certain gene expression patterns were activated, which were quite similar to those patterns expressed during actual human brain development (Renner et al., 2017). As if this were not enough, other scientists quickly jumped on the bandwagon and applied it to their own research. They even improved the model and started to combine it with other established techniques such as single-cell RNA sequencing (Bhaduri et al., 2020; Birey et al., 2017; Di Lullo & Kriegstein, 2017; Pollen et al., 2019; Sloan et al., 2017; Velasco et al., 2019). The most important thing to know about it is that it allows scientists to get an idea of what individual cells in a lump of cells are doing. Quite astonishing when you think of the fact that tissues contain millions of cells. Anyway, the development of these organoid models has rapidly progressed in recent years and it has allowed us to gain great insight into human brain development and neurological disorders. Not just neurological, no, no: Organoid models of numerous, if not all, organs exist. In fact, the very first organoid model was not a brain organoid, but a gut organoid (Sato et al., 2009) (discovered by this Clever(s) man). Regardless of the kind of organoid, or even organoid models in general, I think it can be said that medical science is on an exponential growth curve with new techniques being discovered almost daily. And with that I would like to end this introduction and dive a little deeper in my own PhD project about Alexander Disease.

Alexander Disease (AxD) is a fatal leukodystrophy caused by de novo mutations in GFAP encoding for glial fibrillary acidic protein (GFAP)(Brenner et al., 2001). This mutated GFAP gets cleaved by caspases (Battaglia et al., 2019) and