

Psychedelic Assisted Psychotherapy for the Treatment of Gender Dysphoria.

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In this issue, Pullara [1] describes the case of a young adult male patient who was diagnosed with Gender Dysphoria (GD) and who had begun the process of both socially and medically transitioning. This transition period was marked by intense feelings of emotional distress, anxiety, depression, and suicidal thought processes, which are all too common among individuals diagnosed with GD [2]. The patient acting on his own and without proper medical supervision, which this journal does not endorse, took 300 μ g of LSD and had a meaningful psychedelic experience, which caused the temporary resolution of his suicidal thoughts and led to the decision to completely desist in the transition process. To our knowledge, this is the first-ever reported case in which symptoms of GD have been improved or resolved after the use of a psychedelic substance.

Despite an estimated prevalence of 390 cases per 100,000 adults in the US [3], GD remains both a highly contentious and disproportionately discussed subject not only within the world of Psychiatry but in society at large. Relative to other psychiatric conditions, there exists only limited long term evidence for the current treatment regimens of hormone replacement therapy (HRT) and gender reassignment procedures (GRP). Further research will be needed and is currently ongoing to determine whether the outcomes of these interventions have been successful. Successful studies will have to adequately control for confounding variables like the known co-morbidities of GD which include: childhood maltreatment [4], substance use disorders [5,6], physical or emotional abuse [7], personality disorders [8,9], sexual assault or abuse [4,10], and other psychiatric conditions such as depression and anxiety [8,11,12]. Also, there has

been a reported increase in GD among females diagnosed with Autism Spectrum Disorder (ASD) [13], which raises the concern for social contagion like effects among this vulnerable population. All of this information ultimately leads one to question whether one size fits all treatment regimen of HRT and GRP is appropriate for every individual diagnosed with GD or whether an alternative approach aimed at addressing those aforementioned issues would be more prudent.

Desistance rates, per the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) V, for individuals diagnosed with GD in childhood or adolescence, is at least 70% and reportedly as high as 98% in natal males and at least 50% and as high as 88% in natal females [14] by age 18 when this cohort is not started on HRT. Couple this with additional studies that show desistance rates of 73-98% [15,16,17], and it is clear that a majority of children and adolescents diagnosed with GD will remit by adulthood provided that no significant interventions are undertaken. However, this means that a not insignificant percentage of individuals will continue to suffer from the symptoms of GD and will require further treatment and management. Both HRT and GRP have shown mild to moderate improvements in certain symptoms of GD, specifically self-reported feelings of gender dysphoria, quality of life metrics, and psychosocial function [18]. Unfortunately, other large-scale, long-term studies looking at the objective measures of psychiatric morbidity, suicidal behaviors, and mortality have shown that individuals who underwent HRT and GRP were still at a substantial risk.

One study showed that post-transition patients were at an almost three times higher risk of all-cause mortality, an approximately four times

higher risk of psychiatric admission, and 19 times higher risk of attempting suicide [19]. Additionally, HRT has several risks associated with its use, including an increased risk of myocardial infarctions in female to male GD patients [20] and an increased risk of cerebrovascular accidents and venous thromboembolism in male to female GD patients [20,21]. Long term data on the effects of HRT is also lacking because most studies only obtain data and results from a 6-12-month period with only a few studies reporting data from patients who have been on HRT for greater than five years [22]. These studies, like most studies on GD patients, suffer from several methodological flaws stemming from small population sizes that result in underpowered studies, response bias due to the utilization of self-reported surveys, and moderate to large attrition biases. GRPs are also associated with several significant post-operative conditions such as normal general surgical risks of infection, bleeding, and adverse reaction to anesthesia. Additionally, GRP can also result in genitourinary and sexual dysfunction, wound healing disorders, gastrointestinal injuries to the rectum or colon, nerve injuries, disappointment in cosmetic appearance, and possibly minor or major regret [23,24]. Though with improved surgical techniques, the incidence of these complications is becoming less frequent.

While these results are far from conclusive, it does not mean that adequately screened and selected patients with GD would not benefit from HRT and GRP. The adverse effects of HRT and GRP do, however, raise the question of how to best manage the remaining patients with GD who, if started on HRT and GRP regimens, would be more likely to have adverse outcomes and less likely to benefit. It is in this patient population that psychedelics like Lysergic Acid Diethylamide (LSD) and Psilocybin might be able to offer an additional treatment option. Psychedelics have shown significant promise in the treatment of treatment-resistant depression [24,25,], PTSD [26],

and suicidal ideation [27] and it is reasonable to hypothesize that if they were used therapeutically, in appropriately chosen patients suffering from GD that they may offer a benefit insofar as they could potentially lead to an improvement or resolution of the feelings of GD or, at the very least, mitigate symptoms of associated co-morbid psychiatric conditions.

The prospective use of psychedelics for the treatment of GD is also in line with previous research investigating the potential use of psychedelics for the management of eating disorders like Anorexia or Bulimia Nervosa [28], Body Dysmorphic Disorder [29], or Obsessive-Compulsive Disorder (OCD) [30]. All of these conditions involve distressing feelings caused by either false beliefs about one's body image or an inability to quell obsessive thoughts, which are similar to some extent with the symptoms experienced by patients with GD.

Classic psychedelics, such as LSD, Psilocybin, Mescaline, and DMT, exert their neuropharmacological effects on the brain via binding to serotonin receptors, specifically 5HT_{2A}, causing a neurochemical cascade [31,32] culminating in alterations to Resting State Networks (RSN). RSNs are "structured patterns of resting-state functional connectivity" regions of the brain that are highly active during perceptual or cognitive performance tasks [31,33]. The Default Mode Network (DMN) is one such RSN and is more active in the absence of goal-directed activities and "metacognitive" processes that are hypothesized to be at least partially implicated in the formation of the "ego" [31,34,35]. The major neurochemical effects of the classic psychedelics appear to decrease or weaken activity in the DMN [31,36] and overall increase connections and activity between different RSNs [31,37] resulting in the prototypical subjective experiences of perceptual disturbances, increased emotional access, and ego dissolution. With ego dissolution being a significant predictor of positive experiences [31]. Ego dissolution and increased emotional access to feelings of forgiveness, trust, empathy, and

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acceptance are the two most promising factors with implications for the treatment of GD. For the subset of GD patients who, as previously mentioned, have co-morbid psychiatric conditions, suffer from substance use disorders, or experienced significant trauma or abuse the potential benefits from increased emotional processing and decreased ego interference due to the effects of a psychedelic substance could be sizeable, especially when used in association with psychotherapy, because of the high degree of emotional dysregulation and immature ego defense mechanisms that are commonly seen in these types of individuals.

Psychedelic use is contingent on the mindset of the patient, which is at least if not more important than the physical setting in which the experience takes place. The mindset is established in the weeks or months before the experience. This preparatory work gives time for the patient and the therapist to develop a therapeutic rapport, which is the most important aspect of psychotherapy, and without which an experience should not be attempted. During this preparatory phase, a patient's biological and psychosocial factors that could potentially result in a negative experience are noted. The patient is also encouraged to reflect on their life and, if feasible, write an autobiography. At the very least, a patient should develop a list of questions surrounding a particular problem for which they would like answers [38]. These activities prime the mind for the psychedelic experience, which reduces the likelihood of a negative experience.

The combination of psychotherapy in conjunction with Psychedelic substances often results in a rapid and deeply significant psychological experience that is associated with improvement or resolution of the prespecified intention of the session. The implications for use in GD patients are vast, but at a minimum, psychedelics could offer diagnostic clarity in patients with unclear GD diagnoses. For patients in whom the symptoms of GD seem to be inconsistent or questionable compared to the clinical picture or patients with significant co-

morbid conditions such as ASD, OCD, PTSD, or personality disorders. Especially if there is a concern that these conditions are exacerbating GD symptoms, which decreases the likelihood that a patient would be able to complete the standard regimen of HRT and GRP. Additionally, psychedelics could help determine the primary driver of symptoms, if there is a concern that the GD is not the primary diagnosis but rather a manifestation of some underlying conditions such as the social contagion effect seen in ASD patients with Rapid Onset GD [4].

Psychedelics offer an alternative approach that could be used in GD patients to further assess their appropriateness for HRT and GRP in the one to two years before the initiation of this process. This would theoretically reduce the rates of regret post-transition that some patients with GD experience. Psychedelics are extremely safe, and when done in appropriate settings with adequate supervision, there is little risk of negative experiences or adverse events. However, some patients should not use Psychedelic substances, specifically those with a psychotic illness such as Schizophrenia, Bipolar I Disorder, and similar psychotic illness. Beyond these exceptions, Psychedelics can be used in most patient populations with the caveat that thorough histories should be obtained with particular attention paid to screening for cardiovascular disease and family history of severe psychiatric illnesses. Medication reconciliations are imperative to reduce and avoid adverse drug events such as serotonin syndrome. Administration facilities should be equipped to handle common adverse events such as anxiety, nausea, or paranoia and develop contingency plans for severe reactions or behaviors [39]. Lastly, the potential of developing Hallucinogen Persisting Perception Disorder (HPPD) is relatively rare, with an estimated prevalence of around 4%. While it is theoretically possible to develop HPPD after any use of a hallucinogen or psychedelic, it is more common in frequent heavy users and relatively

rare in clinical trial data where psychedelics are used at appropriate doses and intervals [40].

Psychedelics offer a potentially novel treatment modality for persons diagnosed with GD who, after appropriate psychiatric evaluation, are thought to incur far more risk than benefit in the current standard regimen of HRT and GRP. GD patients with co-morbid substance use disorders, a history of previous trauma or abuse, chronic suicidal thoughts, and or other psychiatric conditions, could likely benefit from Psychedelic associated Psychotherapy when it is utilized in an evidence-based manner with patients who are in the proper mindset and physical setting to best facilitate a positive and productive experience.

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