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An independent academic psychologist, based in England, who has written extensively on different areas of psychology with an emphasis on the critical stance towards traditional ideas.

A complete listing of his writings at http://psychologywritings.synthasite.com/. See also material at https://archive.org/details/orsett-psych.

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1. PSYCHIATRIC SIDE EFFECTS OF STEROID THERAPY WITH PARTICULAR REFERENCE TO MANIA

1.1. INTRODUCTION

Corticosteroids, which include glucocorticoids (GCs) and mineralocorticoids [1], are "a class of chemicals encompassing both laboratory-synthesised and naturally produced hormones [2]. They produce a myriad of important biochemical and physiologic effects on various tissues throughout the body. Glucocorticoids, in general, regulate metabolism and inflammation; mineralocorticoids regulate sodium and water levels" (Oray et al 2016 p457).

Common non-psychiatric side effects of corticosteroid therapy includes weight gain, infection, and hypertension (Brown and Chandler 2001) [3]. "Although the physical manifestations of corticosteroid excess are well-documented, the neuropsychiatric side-effects (often termed 'steroid psychosis') are less well defined" (West and Kenedi 2014 p201). The first documented report of psychiatric symptoms as a side effect of steroids was published by Rome and Braceland (1950), according to Niebrzydowska and Grabowski (2022). At the same time, Boland and Headley (1950) "noted that even after small doses of cortisone, almost every patient 'experienced some psychic change'" (Dubovsky et al 2012 p105).

Subsequently, Rome and Braceland (1952) classified four grades of psychiatric side effects of steroids based

[1] "They are named for their effect on carbohydrate metabolism" (Dabbah-Assadi et al 2022 p363).

[2] Synthetic versions of natural steroid hormones produced by the adrenal cortex (Rahman et al 2023). Edward Kendall isolated cortisone in the late 1930s, and Philip Hench used it with rheumatoid arthritis in the late 1940s (Warrington and Bostwick 2006). Over ten million new corticosteroid prescriptions per year covering almost 1% of the general population (Warrington and Bostwick 2006).

[3] Studies vary in their definitions of side effects. Warrington and Bostwick (2006), for example, used "clinically significant symptoms as those that disrupt patients' daily lives or cause duress to them or those around them" (p1362), while severe reactions are "serious enough to require psychiatric advice and treatment" (Smyllie and Connolly 1968 quoted in Warrington and Bostwick 2006).

on twenty patients receiving cortisone and adrenocorticotropic hormone:

1 - Mild euphoria, lessened fatigue, and improved concentration, energy, and clarity of thought.

2 - Heightened euphoria, hypomania, with restlessness, insomnia, increased motor activity, and accelerated mental activity.

3 - Various including anxiety, and depression, and mood swings (from hopelessness to excitement).

4 - "grossly psychotic" (quoted in Grover et al 2021), and "extreme variations in mood" (quoted in Dubovsky et al 2012).

Since this time other (neuro)psychiatric side effects have been observed as well (Grover et al 2021).

Naranjo et al (1981) developed an algorithm of causality for drugs and side effects (table 1.1).

- Symptoms present before starting the drug.
- Symptoms appeared after drug started.
- Symptoms stopped after drug cessation.
- Symptoms reappear if drug restarted.
- Alternative possible causes of symptoms.
- Symptoms confirmed objectively.

(Based on table 1 p521 Roxanas 2018)

Table 1.1 - Key elements of Naranjo et al's (1981) algorithm of causality of side effects.

1.2. GLUCOCORTICOIDS

GCs were introduced in the 1950s, and have been used effectively with allergic and inflammatory conditions

(Alsalem et al 2022) [4] [5].

Oray et al (2016) provided an overview of the side effects of of GCs from peer-reviewed literature published in English at that time. Commenting on the studies, the researchers noted that most were retrospective and observational, with the need for more randomised controlled trials (Oray et al 2016).

Dubovsky et al (2012) described the adverse effects of GCs as "legion" (p103). All areas of the body are impacted in terms of side effects of GCs, grouped as musculo-skeletal (eg: oesteoporosis), gastro-intestinal (eg: gastritis), cardiovascular, and endocrine and metabolic. The neuropsychiatric side effects of GCs include mania, depression, anxiety, psychosis, and cognitive decline, both after short- and long-term use (Alsalem et al 2022) [6]. Fardet et al (2007) reported such side effects in half of patients taking more 20 mg/day of prednisone for more than three months.

In a review of studies on short-term GC use (ie: less than thirty days), Noetzlin et al (2022) found the incidence of psychiatric side effects varied from 2% to 60% of samples depending on definitions and clinical situations.

Specifically, Alsalem et al (2022) described a case study of mania after use of GC eye drops (prednisolone) post-cataract surgery by a 75 year-old woman in Saudi Arabia (with no prior history of the condition or any psychiatric disorder). The mania, which included elated mood, restlessness, insomnia, and talkativeness, was reported by family members to have appeared two days after initiation of the eye drops. Discontinuation of the eye drops led to reduction of mania symptoms within a week. Only four other cases had been published of GC eye drops (prednisolone and fluorometholone) and psychiatric side effects, according to Alsalem et al (2022). Three cases involved adults over 70 years old, and one 15 year-old male, and all made a full recovery after stopping the eye drops (appendix 1A). Two of the individuals had a past history of psychiatric problems.

In another study in Saudi Arabia, Alturaymi et al

[4] In cancer, for example, corticosteroids are used to alleviate pain associated with inflammation (Kusljic et al 2016). With steroids specifically for cancer patients, Ismail et al's (2017) review found mostly case reports (19 of 25 studies included), and it was not possible to produce an exact prevalence of steroid-induced neuropsychiatric effects. The figure of 5-10% was the range of prevalence.

[5] "In neurons, the glucocorticoid-glucocorticoid receptor complex has been shown to translocate to the nucleus and alters neurotransmitter gene transcription, resulting in alterations in the production of dopamine and serotonin, as well as neuropeptides such as somatostatin or beta-endorphin" (Noetzlin et al 2022 p5).

[6] Manic symptoms can appear immediately after the first dose, whereas depressive symptoms are associated with long-term use or after discontinuing the GC treatment (Noetzlin et al 2022).

(2023) reviewed the medical records of all patients at one hospital between 2016 and late 2022 using oral corticosteroids for more than four weeks (n = 3138). The overall prevalence of any mental disorder was 5.5%, but for individual disorders the figure was below 1% (eg: anxiety disorder 0.95%).

Bolanos et al (2004) undertook a study of long-term prednisone use (at least six months) for asthma or rheumatic illness with twenty patients (and fourteen controls with similar illnesses but no corticosteroid use). Psychiatric symptoms were assessed by a clinician as well as with self-reported measures, including the "Internal State Scale" (ISS) (Bauer et al 1991). This is a series of 100-point visual analogue scales covering activation (manic symptoms - eg: "Today I feel impulsive"), perceived conflict, well-being, depression, and global mood.

Overall, 20% of the prednisone group had a medication-induced mood disorder (clinician-rated), and there were significant differences on the self-report scales compared to the controls. Based on the latter, 60% of the medication group met the criteria for mania or hypomania ("a typically milder version of mania" [7]), and 15% for depression compared to one individual in the control group for the former condition. The difference between clinician and patient measures suggested that cases may be missed if the former method only is used.

Cross-sectional data from a small sample were key limitations of this study. "Strengths of the study include the use of a control group with similar medical conditions, age, sex and level of education, the use of both clinician-rated and self-report measures of mood, and the use of a structured diagnostic interview" (Bolanos et al 2004 p504).

In terms of risk, Fardet et al (2012) calculated the hazard ratio for oral GC, after controlling for age, gender, practitioner, and underlying medical condition, as 4.35 greater for mania compared to controls, and 6.89 for suicide and attempted suicide using a large UK dataset.

Noetzlin et al (2022) offered some guidelines for health professionals for GC use (table 1.2).

[7] See https://www.mind.org.uk/information-support/types-of-mental-health-problems/hypomania-and-mania/about-hypomania-and-mania/.

- Prescribe the lowest dose for shortest period possible.
- Choose the right GC for the right disease.
- Consider interactions with other drugs.
- Be aware of underlying conditions that increase the risk of GC side effects.
- Provide the patient with information about possible problems.

Table 1.2 - Some recommendations around GC use.

1.3. CORTICOSTEROIDS

More generally, three reviews with a total of 122 cases (reviewed by Lu et al 2021) found that around 5% of patients had severe psychiatric reactions after steroid use. The median time of onset of such symptoms was 11.5 days after initiating steroids, with around one-third of patients having onset within one week (Lu et al 2021).

Kenna et al (2011) found fifty-five cases of psychiatric disorders with corticosteroid medication. Further analysis of these cases by Rahman et al (2023) noted that over half were hypomania or mania.

Brown and Chandler (2001) found six studies (with clearly defined diagnostic criteria, and not including case reports) published between 1996 and 2000 on psychiatric symptoms after corticosteroid therapy. The highest prevalence of mania was reported in one study of fifty ophthalmologic patients taking a short course of high-dose steroids at 26% (while 10% developed depression) (Naber et al 1996). Brown and Chandler (2001) commented: "In all cases, the symptoms began within the first three days of therapy and continued throughout the eight days of the study. Gender, age, or history of prior corticosteroid treatment did not predict response. These findings suggest that symptoms of mania are more common than depression during short courses of high-dose steroids" (p18) [8].

Naber et al (1996) was a prospective study, like most of the others, but with fewer participants taking corticosteroids for various conditions. The Boston Collaborative Drug Surveillance Programme (1972) was an exception among the six studies reviewed by Brown and Chandler (2001) with 676 patients. This study found that with low doses (less than 40 mg/day of prednisone),

[8] There are studies showing that corticosteroids as a treatment improve depressive symptoms, for instance (Dabbah-Assadi et al 2022).

psychiatric symptoms were rare (1.3%), but higher (18.4%) with higher doses of corticosteroids (above 80 mg/day), thereby "strongly supporting that these symptoms are dose dependent" (Brown and Chandler 2001 p18).

Fardet et al (2012) noted over 10 000 cases of severe neuropsychiatric symptoms over a eighteen-year period with an incidence of 22.2 per 100 person years for first-course corticosteroid treatment (West and Kenedi 2014). This study used "The Health Improvement Network" (THIN) database on anonymised electronic medical records from general practice in the UK (n = 372 696 patients).

Warrington and Bostwick (2006) observed: "The substantial variability in reported incidence reflects the unpredictability of these reactions, the large variations in researchers' definitions of reactions, the wide range of doses, and the diverse patient groups" (p1362).

Risk factors for steroid-induced psychopathology included (Lu et al 2021):

a) Dose (ie: higher).

b) Concurrent drugs (particularly those that increase corticosteroid levels) [9].

c) Female ("perhaps due to greater propensity in women to seek medical care or a higher prevalence of women with medical disorders that are treated with steroids"; Lu et al 2021 p35).

d) A previous history of psychiatric disorder.

e) Liver or kidney dysfunction.

f) Increased permeability of the blood-brain barrier.

Lu et al (2021) admitted that "the exact mechanism by which steroids induce psychiatric symptoms is unknown" (p34). However, there are hypotheses, including reductions of certain biochemicals like corticotropin and noradrenaline/norepinephrine, or the impact on brain regions like the hippocampus (associated with memory) [10] (Lu et al 2021). One suggestion is that corticosteroid

[9] "Several case reports describe corticosteroid abuse or dependence driven by the euphoria these medications can induce" (Warrington and Bostwick 2006 p1364).

[10] Animal studies find neuronal death in the hippocampus after use of corticosteroids (eg: prednisolone) (Kusljic et al 2016).

action in the brain impacts the neurotransmitter serotonin, which is involved in mood, cognition, and behaviour (Kusljic et al 2016).

A "natural experiment" for corticosteroids is the case of Cushing disease, where excess cortisol (the body's corticosteroid) is produced by a pituitary gland tumour, and one study (Haskett 1985) found that "both depressive and manic symptoms appear early in the illness and only depressive symptoms observed later in the illness" (Bolanos et al 2004 p500).

1.4. STEROID PSYCHOSIS

"Steroid psychosis" has been coined to describe "the development of serious mood and behavioural changes following treatment with corticosteroid medication" (Wolkowitz 1994 p234). Though Dubovsky et al (2012) noted the term "steroid psychosis" as being used in reference to "a heterogeneous mixture of neuropsychiatric effects, most of which do not involve psychosis" (p103).

Wolkowitz (1994) detailed a number of studies that he had been involved in performing that administered steroids to animals or medically healthy humans. For example, Wolkowitz et al (1985) involved thirty-five volunteers given the corticosteroid medicine dexamethasone, and it was found that increased corticosteroids increased dopamine, which "may influence vulnerability factors for experiencing psychotic symptoms with chronic steroid treatment, although acute and chronic effects are very likely different" (Wolkowitz 1994 p236). The increased dopamine may be a consequence of hypothalamic-pituitary-adrenal axis suppression (Niebrzydowska and Grabowski 2022).

Wolkowitz et al (1990) administered prednisone (80 mg) to twelve healthy volunteers for five days. The medication was "associated with few consistent, significant behavioural changes, although most individual volunteers did note or display some alteration in mood or behaviour" (Wolkowitz 1994 p238).

Psychotic side effects have been reported with other medications, including anti-epileptic drugs (eg: 6% of users), anti-malaria drugs (eg: 3%), and anti-retroviral drugs (Niebrzydowska and Grabowski 2022).

1.5. COVID-19 PANDEMIC

Indiscriminate self-medication with steroids was an issue in the early days of the covid-19 pandemic. Grover et al (2021) reported two hospitalised cases:

1. "Mr A" (25 year-old male) - showed steroid-induced mania: "He would try to remove his oxygen mask, not lie down still, and come out of bedtime and again, due to which he had to be physically restrained. He would become angry about being restrained and try to break the restraints [...] On mental state examination, at the time of presentation to our centre [in India], the patient was euphoric, with occasional irritability, and had grandiose delusions of ability and association. He was distractible, able to recognise his relatives, and was well oriented to place. He would not sit still and would become abusive when attempts were made to de-escalate" (Grover et al 2021 p2).

2. "B" (31 year-old male) - showed steroid-associated psychosis: "While being shifted to our hospital, on the way while they had stopped briefly, he jumped into a nearby river and had to be rescued, resuscitated, and brought to our centre [...] During the hospital stay, initially, he had sleep disturbance, became irritable with the family members, and heard that he would die. His physical health condition improved in 6 days, and he was sent for home isolation. However, by the seventh day, he started to remain fearful, the voice that people are trying to harm him, speak irrelevantly, and often voice about the difficulty in breathing" (Grover et al 2021 p2).

1.6. NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Individuals with psychiatric disorders who suffer physical health co-morbidities often have multiple medication use (polypharmacy). For example, the use of non-steroidal anti-inflammatory drugs (NSAIDs) for the physical health condition, which may interact with the psychotropic medication (eg: with selective serotonin reuptake inhibitor (SSRI) anti-depressants). The evidence, however, is not conclusive here (Kohler-Forsberg et al 2017).

For instance, the "Genome-Based Therapeutics Drugs for Depression" (GEN-DEP) trial did not find any impact of NSAIDs on anti-depressants among 811 depressive

participants over twelve weeks (Uher et al 2012).

Similar results came from the "Clinical and Health Outcomes Initiatives in Comparative Effectiveness for Bipolar Disorder Study" (Bipolar CHOICE) (Kohler-Forsberg et al 2017). The participants were 482 individuals diagnosed with bipolar disorder, followed for six months. Around one-third (n = 177) were taking NSAIDs or paracetamol during the study period. All participants were prescribed mood-stabilising medication (eg: lithium; quetiapine). Nine data collection points occurred, and 382 participants completed them all.

There was no difference found in bipolar disorder outcomes at six months between individuals taking NSAIDs or paracetamol and those not.

While Rosenblat and McIntyre (2017) noted that "the effect of NSAIDs in bipolar depression remains unclear as clinical studies have yielded mixed results" (p10).

In terms of longer studies, an analysis of ten years of data in Denmark (Kessing et al 2019) found that non-aspirin NSAIDs were associated with increased incidence of bipolar disorder. One confounder was that "non-aspirin NSAIDs are primarily used for moderate to severe pain, and... pain increases the risk of diverse mood and anxiety disorders" (Kessing et al 2019 p415).

1.7. BIPOLAR DISORDER

Concentrating on bipolar disorder (BD), Rodrigues Cordeiro et al (2022) performed a review of 108 studies on the risk factors for relapse and/or acute mood episodes. Steroid medication was not reported in any of the studies, but one case report mentioned naproxen (NSAID) (Jiang and Chang 1999) [11], and another anti-obesity treatment with fenfluramine and phentermine (Zimmer and Gregory 1998).

Generally a wide selection of risk factors were found, including anti-depressants, sleep disruption, stressful life events, brain stimulation, energy drinks, hormonal changes, and viral infection.

One problem, according to the researchers, was the failure of studies to distinguish between risk factors for onset of BD and for relapse episodes.

From a different angle, Horrobin and Lieb (1981)

[11] This article reported five cases of patients with existing mental disorders (one bipolar disorder, two depressive disorder, one schizophrenia, and one with anxiety disorder) who developed moderate-to-severe depressive symptoms with use of NSAIDs for rheumatoid illness in Taiwan.

proposed the hypothesis that immune dysfunction may be a mediator in the development of BD. A key piece of evidence is the high rate of inflammatory medical conditions (eg: autoimmune disorders) that are co-morbid with BD. Though the nature of the relationship has not been established - ie: "immune dysfunction may be a common underlying cause of both BD and an inflammatory co-morbidity in a given patient. Alternatively, BD may proceed the inflammatory condition or vice versa. All three scenarios are observed in the BD population suggesting that the interaction is likely bidirectional in that immune dysfunction, BD and inflammatory co-morbidities may be perpetuating each other" (Rosenblat and McIntyre 2017 p2).

For example, rheumatoid arthritis (RA) has a co-morbidity with depression (14-48% of RA patients) (Mandaci et al 2022). The nature of the relationship, however, is not entirely clear. For instance: "Both the stress caused by the disability resulting from the general deteriorating course of the disease and the effects of the drugs used in the treatment of RA may trigger several types of mood disorders" (Mandaci et al 2022 p138).

One issue is whether the psychiatric disorder is diagnosed before or after the diagnosis of RA. One study found an increased risk of BD in the first four years after RA diagnosis, while study reported a higher rate of BD in the 2-3 years before RA diagnosis than in controls (Mandaci et al 2022).

The drugs used to treat RA may lead to psychiatric side effects as an example, while the pain and fatigue experienced with RA can have negative mental health effects.

In a meta-analysis, Stubbs et al (2015) found that the prevalence of pain was nearly 30% among individuals with BD, which was calculated as twice the risk of controls.

BD and chronic pain was associated with slower psychiatric recovery, greater functional incapacitation, lower quality of life, and increased risk of suicide compared to BD sufferers without pain or controls (Stubbs et al 2015).

The co-morbidity of pain with bipolar disorder is important because of the prescription of medication to deal with the pain, and their psychiatric side effects. Stubbs et al (2015) commented: "For instance, in the general population chronic pain is often managed with tricyclical anti-depressants, yet prescription of such

medication to a person with bipolar disorder may inadvertently trigger a manic phase of illness if prescribed in the absence of a mood stabiliser. Commonly used analgesic medications also need careful consideration. For instance, there is sound evidence that non-steroidal anti-inflammatory medications can increase serum lithium levels, impairing renal lithium excretion and possibly eliciting lithium toxicity. Similarly, some stronger analgesic medications such as opioids may have mood altering qualities increasing the risk of eliciting a manic episode" (p85).

Stubbs et al (2015) found twenty-two cross-sectional studies for their meta-analysis, covering over 17 000 individuals with BD. There were some common methodological issues with the studies, including:

i) The measurement of pain, including type, location, and severity.

ii) Sampling - eg: the use of clinical samples who are more impaired and reported more pain than non-clinical samples due to self-referral for treatment. This is described as "Berkson's bias" (Stubbs et al 2015).

iii) Age, and gender composition of samples.

iv) Method of diagnosing/measuring BD.

v) A control group or not.

1.8. QUALITATIVE RESEARCH

Clifton et al (2018) interviewed eighteen newly diagnosed or newly relapsed Australian cancer patients about their experiences taking high dose steroids. Telephone interviews lasted up to one hour. The side effects varied - negligible (33%), mild (37%), moderate (17%), and severe (11%) - and included paranoia, aggressiveness, sleep disturbances, and changes in body image. Noteworthy was the finding that "steroid side-effects of heightened energy and weight gain could respectively counterbalance cancer's pain, mobility, fatigue, and weight-loss effects which could please participants" (Clifton et al 2018).

Participants seldom recognised the psychological changes as due to the steroids (ie: misattribution of cause). They were left to self-manage the negative effects with adverse repercussions for family members

sometimes. The researchers recommended educational preparation for the psychiatric side effects.

A quote from "Participant 18" gives a flavour of the findings: "The first week I had the treatment I was really sort of – I don't know, a bit shaky, aggravated, anti, sort of very short fused... the second week - well after treatment I was the complete opposite. I was like depressed, sad, in a state of like just sooking up all the time... The third week well I was the complete opposite again... I went back to like being angry, being obnoxious, being very unkind, short fused again, very horrible to be around. And the last treatment I've just had was the best treatment I've had, I've actually been normal" (quoted in Clifton et al 2018).

1.9. APPENDIX 1A - CONTINUING SYMPTOMS

Stopping corticosteroids can still leave problems. Freyberg et al (1951) coined the term "post cortisone withdrawal syndrome", which was more common in women, to describe "discouragement and depression" (quoted in Roxanas 2018). Mania after cessation of steroids has also been reported (eg: Cerullo 2008).

Roxanas (2018) reported two cases of the latter. One case was a 67 year-old man who developed manic symptoms while taking corticosteroids, which persisted. The author explained: "When seen three months after stopping CS [corticosteroids] , he was talking incessantly with flight of ideas, was irritable when interrupted, complained of insomnia, but was otherwise courteous and cognitively intact" (Roxanas 2018 p521). The other case (a 72 year-old woman) had symptoms that persisted for four months after stopping prednisone.

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2. SMART DRUGS AND KNAPSACK TASK

Stimulant prescription-only drugs are viewed as "smart drugs" to enhance cognitive performance by students, say. Such drugs improve impaired cognitive functioning, but the evidence is "at best, ambiguous" (p1) around improving unimpaired cognition (ie: an above the normal benefit) (Bowman et al 2023).

One problem is that the cognitive tasks used in experiments are not the same as real-life ones. In their research, Bowman et al (2023) tried to rectify this weakness by using "a task that encapsulates the difficulty of real-life daily tasks: the 0-1 knapsack optimisation problem ('knapsack task')" (p1). This involved participants choosing from a selection of 10-12 items of differing weights and values, which to fit into a weight constrained knapsack (in a computer-based exercise). In four minutes, participants had to pack items to gain the highest value.

Forty Australian students perform the experiment, which involved four "drug" conditions - placebo, methylphenidate (30 mg), modafinil (200 mg), and dextroamphetamine (15 mg). Each condition involved eight instances of the knapsack task varying in difficulty (and two attempts each instance). There was one week between each condition. Participants also performed a series of standard cognitive tasks as used in other experiments.

Each participant was given a score or correct or not for the eight instances of the knapsack task, and overall 50% of instances were correct. Compared to the placebo condition, participants achieved lower total value of the items in the drug conditions, and spent more time inspecting the items in these conditions. More attempts to solve the task occurred in the drug conditions (ie: the number of moves of items on the computer screen). There was no difference in the number of correct solutions in the different conditions. There were individual differences in performance.

Bowman et al (2023) concluded: "Our findings suggest that 'smart drugs' increase motivation, but a reduction in quality of effort, crucial to solve complex problems, annuls this effect" (p1).

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3. IMAGE AND PERFORMANCE-ENHANCING DRUGS

3.1. SELECTIVE ANDROGEN RECEPTOR MODULATORS

Resistance training builds muscle mass and is a popular aspect of fitness in the general population. "However, even with much training and self-discipline, gaining muscle mass and reaching a muscular and toned body is a slow process that takes effort, time, and patience" (Hilkens et al 2021 p2).

Dietary supplements are believed to accelerate the process (eg: use by one-third of gym members in Brazil; Goston 2010). "In reality, however, protein and creatine provide only marginal additional gains in muscle mass with resistance training" (Hilkens et al 2021 p2).

This has led to some gym users seeking substances like anabolic androgenic steroids (AAS), and selective androgen receptor modulators (SARM) [12] [13]. These substances can have negative health consequences. "Regardless, both SARM and AAS, often termed together as 'image and performance-enhancing drugs', are predominantly used to increase muscularity and modify appearance. Particularly the group of young male gym users has been indicated as 'at risk' for the use of image and performance-enhancing drugs" (Hilkens et al 2021 p2) [14].

Social media images of the "perfect" male body add to concerns. "Besides body image, exercise and nutritional behaviour of gym users may also be affected by exposure to fitness-related content on social media, such as images of physically fit peers or fitness influencers performing resistance exercise, promoting

[12] "SARMs are taken orally, increasing ease of use compared to many other PEDs [performance enhancing drugs], which are typically administered through intra-muscular injections" (Hahamyan et al 2023 p291).

[13] Hahamyan et al (2023) noted: "Marketed as research chemicals, SARMs can be legally bought online or in supplement stores and delivered without age restrictions. Google searching ‘where can I buy SARMs’ provides at least ten different websites that deliver SARMs to your doorstep. This lack of regulation leads to poor quality control, which increases potential for harm" (p291).

[14] "Fuelled, at least in part, by the perception that SARMs are safer than anabolic steroids, recreational users are now leveraging the various anabolic proles of different SARMs to selectively achieve results in terms of 'bulking' and 'cutting'. Bulking refers to a muscle-gaining phase that combines a weight-gain diet with intense weight training, whereas cutting refers to a fat-losing phase that combines adherence to a strict weight-loss diet with aerobic exercise and less-intense weight training" (Burmeister et al 2020 p16).

dietary supplements, or advocating a 'bodybuilding lifestyle' [Duplaga 2020]. Striving for these perfectly depicted bodies, conversely, can have undesirable health implications regarding body image and eating disorders" (Hilkens et al 2021 p2). There is plenty of research on social media and body image among women (Hilkens et al 2021).

The long-term effects of SARMs on the body "remain largely unknown" (Burmeister et al 2020). Worryingly, SARMs are taken in the "fitness community" at doses and durations higher than in clinical tests. For example, fitness and bodybuilding websites recommended "Ostarine" at doses ranging from 10 to 30 mg, which is ten times higher than studied clinically (Burmeister et al 2020). There is also the concern about interaction with other substances (including alcohol and recreational drugs). This includes "stacking" (taking more than one type of SARM at the same time) (Burmeister et al 2020).

Clinical testing is usually related to the SARM's original licensing purpose. For example, "Ostarine" was developed in the 1990s for treatment of muscle wasting and osteoporosis, while "Testolene" is used for muscle wasting, and breast cancer (Burmeister et al 2020).

Furthermore, SARMs are purchased via the Internet where there is no quality control. van Wagoner et al (2017) investigated forty-four products marketed and sold on the Internet as SARMs. Analysis of the chemical ingredients found that only half contained SARMs. About one-tenth had no active compound, but one-quarter included substances not listed on the label, and over one-third included other unapproved drugs. Overall, only 40% of the products contained the amount of active compound that matched the listing on the label (Burmeister et al 2020).

Hilkens et al (2021) undertook a study of AAS and SARM use in the Netherlands. A sample of 2269 male gym users and resistance trainers (18-40 years old) were recruited via fitness clubs, gyms, and related online sites.

Resistance training was defined as training with weights, and questions were asked about amount of time spent doing it. Social media use was assessed, including "image-centred social media use" (ISMU) ("ie: "the exposure to fitness-related content on social media and comparing one's physical appearance with others based on this fitness-related social media content"; Hilkens et al 2021 p4) (eg: "When looking at photos of the following

people [a list provided covering celebrities, fitness model, actors, athletes, friends and family] on social media, how often do you compare your physical appearance to theirs?"). Body image was measured by the "Revised Male Body Attitudes Scale" (MBAS-R) (Tylke et al 2005) (eg: "I think I have too little muscle on my body"). Finally, there were questions about use of dietary supplements, and image and performance-enhancing drugs.

Just over 80% of the sample had used dietary supplements in the previous month (eg: protein; creatine; caffeine) (compared to 10% of the general population aged 21-35 years in the Netherlands (eg: "protein shakes"); Wardenaar et al 2016). So, use of "'muscle-building' supplements is highly prevalent among young male gym users" (Hilkens et al 2021 p8).

Concerning AAS, 9% admitted to "ever used" compared to 2.7% for SARMs. A German study (Simon et al 2006) found a prevalence of 12.5% for doping substances generally among regular gym users, while an earlier study in the Netherlands (Stubbe et al 2014) reported 1% for AAS prevalence among both male and female gym users.

Hilkens et al (2021) found that ISMU was significantly associated with supplement use. ISMU had a stronger impact on SARM use than AAS use, but it was significant in both cases. Put simply, "a more negative body image related to increased SARM use" (Hilkens et al 2021 p9).

The study took place during the covid-19 pandemic (in September 2020), "which may have resulted in an under-estimation of the AAS and SARM prevalence rates as a result of the closure of all gyms in the Netherlands preceding this study" (Hilkens et al 2021 p10). The data were self-reported, and correlational.

In summary, the study suggested that "not so much the frequency of social media use may have undesirable effects, but rather the content of social media's images relating to creating a perfect 'me'" (Hilkens et al 2021 p11).

3.2. SOCIAL MEDIA ENCOURAGING USE

A survey of "TikTok" on 2nd June 2021 using the search term "SARMs" produced videos with over 115 million total views (compared to 67.7 million views on 2nd May 2021) (Hahamyan et al 2023). "In mid-June 2021, TikTok banned the hashtags, 'SARMs' and 'Steroids', along with terms for other popular recreational drugs, such as 'cocaine' and 'MDMA'. Hashtags for commonly used SARMs

'Ostarine', 'Testolone', 'Ligandrol', and 'Andarine' were also removed. These actions demonstrate growing concern with the propagation of SARMs information via social media by associating them with drugs with well characterised adverse effects. Following the ban, one cannot search videos by these hashtags, but the content remains available and viewable" (Hahamyan et al 2023 p291).

Meanwhile, "YouTube" has over a thousand videos on SARMs posted in 2020-2022 with over sixty million views, and "Reddit" has communities ("sub-Reddits") on the subject with over 50 000 members (Hahamyan et al 2023) (appendix 3A).

Efimenko et al (2022) surveyed such sub-Reddit members, and over half of 343 respondents who used SARMs had at least one known side effect.

The Internet has allowed like-minded individuals to share experiences. This is seen, for example, in "supportive drug-related communities" (Bilgrei 2019 p852). This can be viewed as part of consumerism in medicine and the empowerment of healthcare users (Bilgrei 2019).

Bilgrei (2019) reported in-depth interviews with twenty-nine male forum members in Norway on two websites - one related to the use of "body-enhancing substances", and the other to recreational drug use. Three main themes emerged from analysis of the transcripts:

a) "Easy exchange of information" - On the forums, interviewees found "abundant information, all within a social milieu where they felt free to discuss their drug use without fear of repercussions" (Bilgrei 2019 p857).

For example, "Ken", on the forum for body-enhancing substances, said: "I started getting some guidance from friends and stuff, but you know, it wasn't much help. Then I started reading on the Internet. There it was thousands of people sharing their advice. It was really the most important thing for me – just google and start reading on the forums. It was really a revelation. (...) Without the Internet I wouldn't been able to gain the same level of knowledge. It would have been impossible. (...) Especially, I learned how to minimise the negative effects. I didn't have a clue, you know, but I learned that I could take clomid to regulate the hormones, arimidex against water retention and nolvadex to avoid bitch tits, you know, crucial knowledge I wouldn't gain without the net" (p857).

b) "Identity-work and stigma" - The forums allowed participants to discuss who they were in relation to their drug use ("identity-work"), and in relation to the wider (negative) attitudes of society.

Bodybuilder "Ragnar", for instance, said: "Before I started using, my only impression was through the newspapers and stuff like that, and that was terrible, you know. But that's the way the media put it – that people should be afraid. They only write about those who do something wrong, you know, they don't write about the majority who don't. It just causes a lot of prejudice and that's the media's fault" (p859).

c) "Empowerment and social support" - This theme can be seen in Knut's" quote (from the general drug use forum): "I think many have thoughts about the forums, you know, that they kind of promote drug use and cause more people to use. I'm not sure, but I think they are really good, because there is so much information that you won't get anywhere else. I've seen hundreds of threads where people want tips on how to inject speed or things like that, and almost instantly, members reply with what I think is safe information. You know, also from people who have had bad experiences, who warn others from doing anything stupid" (p860).

Bilgrei (2019) commented overall: "While there is nothing new about drug users creating communities or sub-cultures where they can share information and learn about drugs, the Internet rather enables a virtual sphere that provides far more effective interaction and communication between users... Though members of the two forums explored in this study were widely different in terms of both drug use and sub-cultural affiliations, their stories were still overlapping – they all sought out the forums in an attempt to gain knowledge and seek a sense of community that exceeded that of their offline lives. While the bodybuilders were concerned with issues relating to physical enhancement, the recreational drug users were concerned with pleasure, sensory impressions and transgression. However, both groups searched the Internet in order to achieve their goals without exposing themselves to unnecessary risk" (p862).

Bilgrei (2019) applied the concept of "community-consumerism" to describe the individuals seeking advice from other users who were classed as important, if not more so, than health professionals and official sources of information. Forum members were perceived as having a specialist knowledge which trumped "official experts".

Bilgrei (2019) ended: "As for the drug users explored in this study, the community-consumerism that characterised the interaction within the forums helped support notions of participants as informed, responsible and empowered..." (p863).

3.3. APPENDIX 3A - USING REDDIT IN ACADEMIC RESEARCH

The view that social media like "Twitter" and "Reddit" are considered "public" is attractive to academic researchers. Zimmer and Proferes (2014) explored this issue for research on Twitter, and Proferes et al (2021) for Reddit.

Concerning the latter, the researchers found 727 studies published between May 2010 and May 2020 that used Reddit as a data source. The most popular academic disciplines were Computer Science, Engineering and Mathematics (figure 3.1).

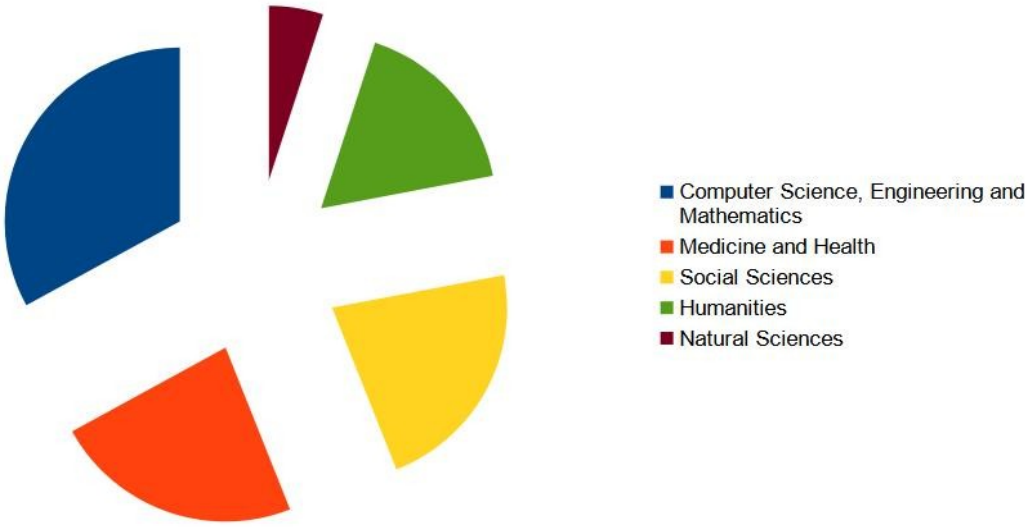

Figure 3.1 - Academic disciplines of published studies using Reddit data (%).

The public nature of posts on Reddit, however, is ambiguous in terms of the Reddit user agreement, while sub-Reddits are user-created and user-moderated. "As part of their sub-Reddit specific-rules, some sub-Reddits carry warnings to researchers about data collection in the communities. For example, r/depression and r/SuicideWatch state all research-related posts and

surveys must be approved by the moderator team, and r/IndianCountry prohibits unauthorised research and requests that anyone interested in using the sub-Reddit for research purposes must complete a form for review by moderators" (Proferes et al 2021 p2).

The most popular sub-Reddits for researchers covered politics, mental health, and drug use. Proferes et al (2021) commented: "This raises questions about why researchers are choosing these specific venues as data sources. Are researchers studying Reddit for the purpose of studying Reddit-specific phenomena, or are they studying social phenomena and the fact the data are from Reddit incidental? From our review of this work, the answer appears to be both" (pp9-10).

Proferes et al (2021) listed some of the general issues with academic researchers using Reddit data:

i) The view that such research does not need an institutional ethics review board application. Most studies noted their "exempt" status here. Proferes et al (2021) responded that "particularly given the potentially sensitive nature of some of the data sources, we suggest that researchers do not simply rely on the adage that just because the data are public, there aren't harms that may stem from the use of the data" (p10).

ii) Whether Reddit's "Terms of Service" prohibit data use or not.

iii) Public/private as a binary. Markham (2012) criticised this assumption as missing that "people interacting online are making more fine-tuned distinctions in reality, not just about whether something is 'public' but also about the use or flow of that information" (Proferes et al 2021 pp10-11).

Proferes et al (2021) found that around one-tenth of the research studies used identifiable Reddit usernames, and about one-third direct quotes. They stated: "While this is a fairly common practice in research papers..., where sub-Reddit content is potentially sensitive (such as when the quote involves mental health, drug use, sexual activity, and is potentially from a minor), there may be outsized safety or privacy risks to those data subjects if their content is shared beyond its intended context" (Proferes et al 2021 p11).

iv) Clarity of details about the dataset used. Some studies obfuscated their data collection methods for

ethical reasons, but around one-third had missing or ambiguous details (eg: "comment" and "post" used interchangeably) (Proferes et al 2021).

v) Reddit uses a sorting algorithm which influences conversation and presentation of material. "For example, as many Reddit users see conversation sorted by its popularity, content that is more broadly agreeable, clever, funny, or even biting is more likely to be responded to... Thus, if a researcher were to scrape every comment from a particular thread, they may end up with a larger volume of data that interact with those 'top posts'" (Proferes et al 2021 p10).

vi) The sample of users. Though demographic information is limited, the users are more likely male, young, and higher socio-economic status than the general population (Proferes et al 2021).

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4. DRUG INFORMATION

Davis et al (2023) began: "To receive and participate in medical care, patients need high quality information about treatments, tests, and services — including information about the benefits of and risks from prescription drugs" (p1). Such information, however, continued these researchers, "is unregulated and has not been evaluated, and it may not be of good quality" (Davis et al 2023 p1).

Davis et al (2023) concentrated on the written information on the benefits of all new anti-cancer drugs approved by the European Medicines Agency (EMA) between 2017 and 2019 (n = 29). Firstly, a set of criteria were developed for assessment based on research studies on patient concerns. These were summarised as:

a) What and who is the drug for.

b) How the drug works.

c) The goal of the treatment with the drug.

d) The type and source of evidence for the benefits of the drug.

e) The benefits shown with the drug.

f) The uncertainties and gaps in the evidence about the drug.

Next the researchers analysed written and electronic sources of information about the drugs, including for clinicians, patients, and the public. The findings were presented under these headings:

i) General information about a drug - Most of the documents provided this information, but the researchers noted gaps in some cases, including "restrictions to the scope of the indication based on mutational status of patients' cancers, disease stage, or the availability of alternative treatment options; the approved combination treatment; and how treatments should be sequenced" (Davis et al 2023 p6).

ii) How a drug was studied - All but one product provided "accurate and full information about the number and design of the main studies, the control arm (if any), study sample size, and primary measures of drug benefit"

(Davis et al 2023 p6). This information was evident in the clinician-related material, but not necessarily to patients or the public.

iii) Drug benefits - Information was provided in the main, but again not necessarily in the patient information leaflets.

iv) Concerns and uncertainties about a drug - Little information here.

Overall, information was more likely provided to clinicians, but not necessarily to the patients or the public. "Both patient facing and public facing sources on drug information often lacked relevance: information on drug benefits was not reported in any patient leaflets, whereas other, potentially less relevant information for patients (ie: the biological mechanism of action) was consistently included" (Davis et al 2023 pp8-9).

Studies with patients show that they want information about the goal of treatment (ie: "whether a drug is intended to prevent or cure disease or to be palliative"; p9), the strength of evidence, and uncertainties about a drug, but this was generally lacking in written form, and "it cannot be assumed that this information will be communicated to patients by clinicians" (Davis et al 2023 p9).

Davis et al (2023) concluded: "Despite the commitment of medicines regulators to shared decision making and person centred care, current regulated sources of prescription information in Europe do not allow patients to distinguish between new anti-cancer drugs that offer clinically meaningful benefits compared with those with considerable uncertainty about effects" (p9).

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5. NEW PSYCHOTROPIC DRUGS, PARTICULARLY ESKETAMINE

Reviewing new psychotropic drugs, Poznanski and Akinyemi (2022) described seventeen medications approved by the United States Food and Drug Administration (FDA) between 2016 and 2022. Three of them for schizophrenia and bipolar disorder, two for adult insomnia, two for excessive daytime sleepiness in narcolepsy, and two for childhood ADHD.

Here are three examples.

Esketamine (trade name: Spravato)

As a supplementary or adjunct for treatment-resistant depression. It is a non-selective, non-competitive antagonist at the the N-methyl-D-aspartate (NMDA) receptor.

Esketamine is chemically based on ketamine, which was used as an anaesthetic in the 20th century. "Ketamine has also been used recreationally from the 1970s, with nicknames 'special K', 'new ecstasy' and 'psychedelic heroin'. At sub-anaesthetic doses ketamine produces a dissociative state that some users enjoy, characterised by a sense of detachment from one's physical body and the external world, often referred to as the 'K-hole' by recreational users. It is usually ingested through insufflation (snorting). A usual recreational dose is between 60 and 250 mg of ketamine" (Horowitz and Moncrieff 2021 p614).

Intravenous ketamine was tested for depression in the 2000s with "rapid-onset anti-depressant effects" (Zanos et al 2018). "It would seem difficult to distinguish this 'rapid-onset anti-depressant effect' from the 'high' or altered state known to be induced by ketamine, however. Although some commentators claim that it leads to a genuine, long-lasting anti-depressant effect, this has not been established in randomised trials, as emphasised in expert guidance" (Horowitz and Moncrieff 2021 p614).

In terms of research on esketamine, for example, in "TRANSFORM-1" (a randomised, double-blind, placebo-controlled trial) (Fedgchin et al 2019), the esketamine group showed clinically significant improvements at four weeks (eg: increased remission of depression symptoms; reduced suicidal ideation) (appendix 5A).

Vasiliu (2023) found fourteen papers for a review of

the evidence on esketamine and treatment-resistant depression [15]. In the main, short-term effectiveness (eg: four weeks) has been established, "but questions about its medium- and long-term action, as well as tolerability profile, remains to be elucidated..." (Vasiliu 2023 p8). Also the risk of abuse cannot be ruled out (Vasiliu 2023).

Table 5.1 outlines three key strengths and weaknesses of esketamine use as it stands in 2023.

STRENGTHS	WEAKNESSES
1. Short-term effectiveness with treatment-resistant depression and supplementary to another anti-depressant. 2. Weekly intra-nasal administration. 3. Compatible with different types of anti-depressants (eg: selective serotonin reuptake inhibitors; SSRIs).	1. Expensive (relative to other anti-depressants). 2. Data lacking on adverse effects and tolerability. 3. Risk of abuse (though data lacking).

(After table IV Vasiliu 2023)

Table 5.1 - Key strengths and weaknesses of esketamine use.

The reporting of adverse events (AEs) (or side effects) of new drugs in pre-approval trials, like TRANSFORM, is crucial. "In 2022, the benefits/harms balance of esketamine is still debated in the scientific literature especially in the long term" (Taillefer de Laportaliere et al 2023 p4305). This is despite the approval of its use in the USA (in March 2019) [16] and in Europe (in November 2019) (but the UK was different [17]) (Taillefer de Laportaliere et al 2023) [18].

"Adverse events... reported in clinical trials play

[15] About one-third of individuals with major depression do not respond to anti-depressants (ie: they are treatment-resistant) (Popova et al 2019).

[16] "The FDA normally requires two positive efficacy trials in order to license a drug, 'each convincing on its own' [Turner 2019]. This requirement has been criticised because short-term trials do not accurately reflect the long periods many drugs are eventually used for in practice and they discount negative trials. However, esketamine did not meet even this standard" (Horowitz and Moncrieff 2021 p615).

[17] It was not initially licensed, but subsequently the "Medicines and Healthcare products Regulatory Agency" (MHRA) did so, while the "National Institute for Health and Care Excellence" (NICE) was against licensing (Horowitz and Moncrieff 2021).

[18] Five studies (including TRANSFORM) were the basis of evidence for esketamine submitted by the makers "Janssen" to the FDA for licensing (Horowitz and Moncrieff 2021).

an important role in characterising the harms/benefits balance. This is even more important when the drug is new and real-life studies are scarce. Thus, the way in which harms are reported in clinical trials becomes essential. The CONsolidated Standards Of Reporting Trials (CONSORT) statement is a tool that guides investigators to improve transparent and quality of publications (Schulz et al 2010). In 2004, this tool was adapted to harms with the CONSORT for harms checklist (Ioannidis et al 2004). According this checklist [sic] , it was possible to quantify the quality of reporting AEs in clinical trials" (Taillefer de Laportaliere et al 2023 pp4305-4306).

Taillefer de Laportaliere et al (2023) reviewed the studies of intra-nasal esketamine and depression, and the reporting of AEs. Data were taken from "ClinicalTrial.gov", which is a publicly accessible database of all clinical trials (as mandated by the FDA in the USA), and the subsequent published articles.

The CONSORT Extension of Harms checklist gives a score between 0-21, with a higher score signifying better quality reporting of harms (table 5.2). Taillefer de Laportaliere et al (2023) found ten trials, of which nine were categorised as "low" (a score of 7-11), and the other as "moderate" quality (a score of 12-16).

Taillefer de Laportaliere et al (2023) summed up the findings: "Compared to AEs recorded in ClinicalTrials.gov, we found that 41.5% of serious AEs and 39% of non-serious AEs were not reported in the published articles. Among them, the majority were psychiatric events but also cardio-vascular events and 94% concerned patients from esketamine groups" (p4305).

* Methods section includes a list of AEs with definitions for each:
  - definitions included
  - all or sample of AEs
  - use of validated instrument to report AE severity

* Results section includes absolute risk of each AE:
  - reported separately for drug and placebo groups
  - severity and grading of AEs
  - number of AEs and number of patients with AEs

(Source: table 1 p4307 Taillefer de Laportaliere et al 2023)

Table 5.2 - Example of items from CONSORT Extension of Harms checklist.

So, using the published articles on the clinical

trials of esketamine would miss many of the AEs. Taillefer de Laportaliere et al (2023) stated: "An assessment of the benefits/risks balance of esketamine based on the results reported in trial publications is flawed due to the poor accuracy and completeness of harm data. Added to the lack of transparency regarding unreported AEs in published articles, this raises questions about the speed of esketamine marketing approval" (p4311).

Taking a critical stance, Horowitz and Moncrieff (2021) ended: "It would seem that themes from history are repeating: a known drug of misuse, associated with significant harm, is increasingly promoted despite scant evidence of efficacy and without adequate long-term safety studies" (p616).

Brexanolone (trade name: Zulresso)

Approved for postpartum depression.

Significant improvements in depression symptoms as measured by the "Hamilton Depression Rating Scale" from baseline (within six months of the birth) at sixty hours, and lasting at Day 30 (Meltzer-Brody et al 2018).

Daridorexant (trade name: Quviviq)

Insomnia in adults.

Adults with insomnia disorder randomly assigned to one of two doses of the drug or a placebo for three months (Mignot et al 2022). The outcome measures of wake time after sleep onset, latency to persistent sleep, and self-reported total sleep time all improved with the drug.

Poznanski and Akinyemi (2022) stated: "The field of psychiatry continues to evolve with increasing knowledge of the pathophysiology of psychiatric disorders, and this knowledge will continually lead to the development of more medications with novel mechanisms of actions. Many new and old agents are being explored for the treatment of psychiatric disorders, and the need for effective medications with limited side effects is ongoing" (p261).

APPENDIX 5A - TRANSFORM

Table 5.3 outlines some other key trials with esketamine than TRANSFORM.

STUDY	STUDY	DESIGN	PATIENTS	VS PLACEBO OR ANOTHER DRUG
ASPIRE I	Fu et al (2020)	Double-blind	266	Placebo
ASPIRE II	Ionescu et al (2021)	Double-blind	230	Placebo
SUSTAIN-1	Daly et al (2019)	Double-blind	297	Placebo
SUSTAIN-2	Wajs et al (2020)	Open-label	802	Placebo

Table 5.3 - Key clinical trials with esketamine (other than TRANSFORM).

Note that SUSTAIN-1 was a discontinuation trial (Horowitz and Moncrieff 2021). After sixteen weeks of esketamine and "stable remission", participants either continued or stopped it (ie: given a placebo), and relapse was measured. The assumption is that if participants relapse in their depression, the treatment must have been working. Horowitz and Moncrieff (2021) observed: "This study design is problematic because withdrawal effects from the drug can be mistaken for relapse of depression. Ketamine is recognised to have withdrawal effects, including lowered mood (dysphoria), fatigue, poor appetite and anxiety" (p615).

These researchers continued: "As half (48.7%) of relapses occurred in the first 4 weeks following esketamine cessation, the time most likely for withdrawal effects to occur, and as the relapse rate in the placebo group became 'closer to esketamine with each week', as highlighted by the FDA, confounding of 'relapse' by withdrawal seems likely" (Horowitz and Moncrieff 2021 p615).

There is also the problem of "unblinding". "The absence of esketamine's psychoactive effects would be noticed by participants randomised to placebo and consequent negative expectations would tend to increase their chance of relapse" (Horowitz and Moncrieff 2021 p615).

Furthermore, one study site in Poland was an

outlier. There was 100% relapse among the sixteen participants in the placebo group compared to 33% among the 81 participants of the esketamine group. "It has been demonstrated that if this outlier site is excluded there is no difference between esketamine and placebo..., leading to the conclusion that the findings are 'not robust'" (Horowitz and Moncrieff 2021 p615).

TRANSFORM-1 (Fedgchin et al 2019)

The sample was 346 adults (18-64 years) with diagnosed recurrent major depressive disorder and symptoms self-reported as moderate-to-severe (eg: total score ≥28 on Montgomery-Asberg Depression Rating Scale (MADRS)). Participants were randomised to receive one or two doses of esketamine (via nasal spray) or a placebo twice weekly for four weeks. Participants also took one of four anti-depressants (duloxetine, escitalopram, sertraline, or venlafaxine) to which they had not already had non-response. This part of the trial was open-label (ie: the participants and researchers knew the anti-depressant being taken) whereas the nasal spray was double-blind administered.

Overall, 91% of the participants completed the trial, and the mean reduction in depressive symptoms between baseline and Day 28 was seen in all three groups. The reduction was larger in the drug groups, but not statistically significant compared to the placebo group. The improvement in MADRS scores, however, "exceeded what has been considered clinically meaningful for approved anti-depressants vs placebo" (Fedgchin et al 2019 p617). Note that the reduction in symptoms was best with one dose of esketamine.

The following points of evaluation can be made:

i) A three-fold higher withdrawal in the two-dose group compared to the one-dose and placebo groups (19 vs 6 and 6). "No clear pattern or trend in the reasons for discontinuation was identified and this does not appear to be due to a new or dose-related safety finding" (Fedgchin et al 2019 p624).

ii) The eligibility of enrolment in the trial was determined by independent raters based on diagnosis, severity, and past anti-depression non-response. All participants had greater improvements in symptoms that expected from previous research. "It is conceivable that

the higher response and remission rates observed in the anti-depressant/placebo group may reflect high patient expectation of receiving a novel drug and/or by the frequent, lengthy (ie: in some cases up to 4 hours twice weekly) clinical encounters that exceed the duration of routine office visits" (Fedgchin et al 2019 pp624-625). Thus, a greater improvement in the placebo group would mask the full benefits of the drug.

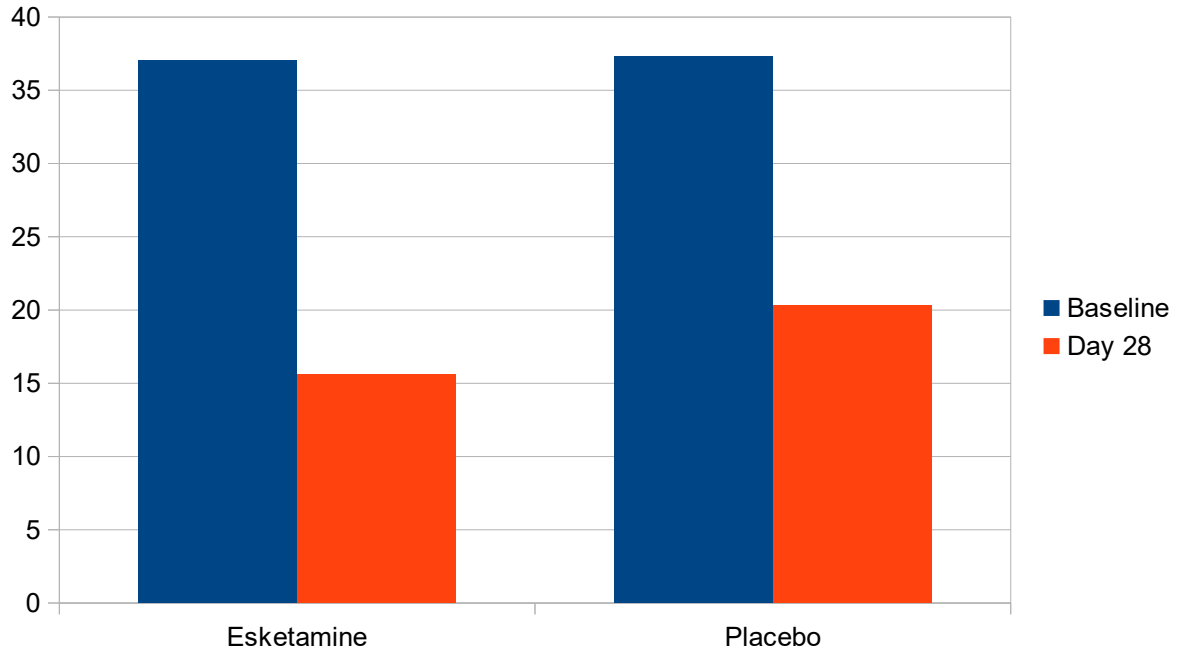
iii) The generalisability of findings limited by exclusion of patients with co-morbid mental disorders, or a serious risk of suicide, while there were more females (two-thirds), and few non-White participants (around 15%) (Fedgchin et al 2019).

iv) A short-term study only (lasting four weeks), which tested as esketamine as an adjunct to another anti-depressant.

TRANSFORM-2 (Popova et al 2019)

Between August 2015 and November 2017 in sites in the Czech Republic, Germany, Poland, Spain, and the USA, 227 individuals with treatment-resistant depression received one of two dose levels of esketamine or a placebo nasal spray (and an oral anti-depressant) for a four-week period. Four weeks of baseline measures were taken prior to the administration of the nasal spray, and there was a post-treatment 24-week follow-up. Six validated measures of depression symptoms were used (eg: MADRS).

One hundred and ninety-five participants completed the four weeks of treatment. "The mean MADRS score decreased from baseline to day 28, with greater improvement observed among those in the esketamine plus anti-depressant arm as compared with the anti-depressant plus placebo arm" (Popova et al 2019 p432) (figure 5.1). Overall, a "clinically meaningful and statistically significant improvement" (Popova et al 2019 p435), though the researchers admitted that the improvement in the placebo group was unexpected. Improvements with esketamine occurred within 24 hours of administration.



(Data from table 2 p433 Popova et al 2019)

Figure 5.1 - Mean MADRS scores (out of 60).

The trial had strict eligibility criteria, which meant similarity in the sample in terms of treatment-resistant depression, but the exclusion of individuals with co-morbid psychosis, for example, limited the generalisability of the findings.

Thirty-nine sites (doctor's/psychiatrist's offices, hospitals and clinics) were involved in the trial in five countries which gave a wider sampling, but they were in Western countries only, and the more centres participating, the greater the possibility of differences in procedure and protocol. The sample was also over 90% White.

The study was double-blind for the nasal spray, but not for the oral anti-depressant. "To maintain blinding, a bittering agent was added to the intra-nasal placebo to simulate the taste of the esketamine solution..." (Popova et al 2019 p430). But Horowitz and Moncrieff (2021) argued that "participants would have been unmasked ('unblinded') by the noticeable psychoactive effects of esketamine (dissociation was reported by the majority of participants); expectation effects might therefore inflate the apparent difference between placebo and esketamine" (p615).

TRANSFORM-3

Turkoz et al (2021) combined the findings of TRANSFORM-1 and 2 in a pooled analysis of 518 patients at day 28. The criteria for treatment response was defined as a ≥50% improvement in MADRS total score from baseline. The pooled response rate was 58.7% of the esketamine group and 45.2% of the placebo group (which is a significant difference at $p<0.001$).

Though some patients showed an early response (at day 2 and/or day 8), those who did not, "can still result in a greater likelihood of response than that observed with an anti-depressant alone" (Turkoz et al 2021 pe7).

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