Beyond the Trip

The Next Wave of Data Capture in Psychedelic Clinical Trials

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With psychedelic therapeutic research gaining momentum, what unique obstacles will we face as Data Managers in capturing data?

1 WHAT ARE PSYCHEDELICS?

Psychedelics are naturally occurring compounds or synthetic drugs such as psilocybin, DMT, LSD, MDMA and ketamine that are said to have '**mind-revealing**' effects.

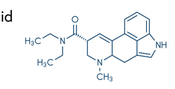
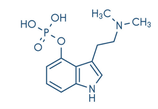
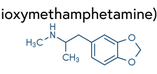
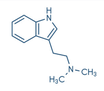
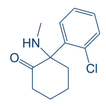
To the public, psychedelics are associated with experiencing a 'trip'. The term 'trip' refers to the hallucinatory experience, with hallucinations being a perception in any sensory modality (including auditory, visual, olfactory, and somatosensory) without an external stimulus.

Hallucination	Origins in the Latin hallucinari meaning 'go astray in thought'
Psychedelic	Origins in the Greek psychē ('soul') and dēloun ('to reveal').

2 PSYCHEDELIC DRUG EFFECTS

Hallucinations are only one aspect of a psychedelic experience. Psychedelic drug effects are wide ranging and difficult to define. MAC Clinical Research therapists' monitoring sessions have documented a range of psychedelic effects such as hallucinations, but also perception disturbances including feelings of experiencing death and time loops. The effect a psychedelic has is dependent on the receptor it has an action on.

PSYCHEDELIC EFFECTS[1]

Psychedelic Compound	Action	Typical Effects
LSD (lysergic acid diethylamide)  LSD	Acts as an agonist on serotonin 5-HT2A receptors	Visual/Auditory hallucinations, Altered sense of time and space, Mystical experiences, Ego dissolution, Synaesthesia
Psilocybin 	Activates serotonin 5-HT2A receptors	Visual/Auditory hallucinations, Altered sense of time and space, Mystical experiences, Ego dissolution, Synaesthesia
MDMA (3,4 - Methylenedioxymethamphetamine)  MDMA	Acts as a releasing agent of serotonin, dopamine, and norepinephrine	Induced feelings of euphoria, Empathy, Openness, Closeness with others
DMT (deuterated dimethyltryptamine)  DMT	Agonist on serotonin 5-HT2A receptors, as well as other serotonin and dopamine receptors	Intense visual and auditory hallucinations, Mystical experiences, Ego dissolution, Contact with other entities
Ketamine 	Antagonist on NMDA receptors	Dissociative effects, such as feeling detached from one's body and environment, Altered sense of time and space, Dream-like states

Sources:
(1) Mackenzie RJ (2021, 16 Nov). An Introduction to Five Psychedelics: Psilocybin, DMT, LSD, MDMA and Ketamine. An Introduction to Five Psychedelics: Psilocybin, DMT, LSD, MDMA and Ketamine | Technology Networks

3 PSYCHEDELIC THERAPEUTIC RESEARCH MOMENTUM

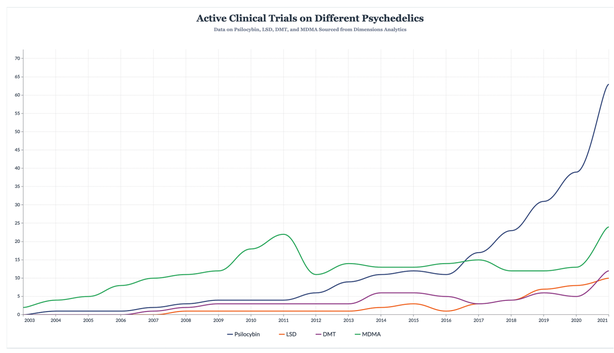
Since the first psychedelic trial of LSD in 1943[2], particularly after the first English language publication on LSD in 1950[3], there has been interest in the positive effect psychedelics may have on mental health.

From the early 1950s, psychedelics (especially LSD) were of great interest in psychotherapy practice and research[4] with studies between 1949 and 1973 showing clinically judged improvement in mood disorders[5] and a reduction in alcoholism that led to LSD being labelled the miracle cure for those with alcohol addiction[6].

In 1970, with increased recreational use and a subsequent increase in hospitalisations, the so called 'war on drugs' resulted in LSD and psilocybin being classified as Schedule 1 narcotics under the Controlled Substances Act in the USA[7], with MDMA following suit in 1985. Psychedelics had shown great promise in the treatment of psychiatric conditions, however, research declined due to a resulting lack of mainstream acceptance.

Since the early 2000s there has been renewed interest in psychedelic research, kicked off by ketamine and MDMA trials that showed these were as effective as conventional psychiatric medications[7] with no addictive effects.

With the FDA granting therapy designation to MDMA and psilocybin as breakthrough treatments for PTSD and depression respectively[8][9] there is increased optimism for psychedelics' positive impact on mental health and there has been a rapid upturn in psychedelic studies being conducted in recent years.



Sources:
(2) MAPS. (2014, Apr 15). First LSD Hallucination: April 16, 1943 - Multidisciplinary Association for Psychedelic Studies - MAPS. Multidisciplinary Association for Psychedelic Studies. https://maps.org/news/media/first-lsd-hallucination-april-16-1943/
(3) Busch AK, Johnson WC (1950). L.S.D. 25 as an aid in psychotherapy; preliminary report of a new drug. Dis Nerv Syst 11: 241–243.
(4) Carhart-Harris RL, Goodwin GM (2017, Oct). The Therapeutic Potential of Psychedelic Drugs: Past, Present, and Future. Neuropsychopharmacology 42(11): 2105–2113.
(5) Rucker JJ, Jelen LA, Flynn S, Frowde KD, Young AH (2016). Psychedelics in the treatment of unipolar mood disorders: a systematic review. J Psychopharmacol 30: 1220–1229.
(6) Chwelos N, Blewett DB, Smith CM, Hoffer A. (1959, Sep). Use of d-lysergic acid diethylamide in the treatment of alcoholism. Q J Stud Alcohol. 1959 Sep;20:577-90.
(7) Reardon S. (2023, 01 Nov). Psychedelic treatments are speeding towards approval – but no one know how they work. Nature.
(8) MAPS. (2017, 26 Aug). FDA Grants Breakthrough Therapy Designation for MDMA-Assisted Therapy for PTSD, Agrees on Special Protocol Assessment for Phase 3 Trials. https://maps.org/news/media/press-release-fda-grants-breakthrough-therapy-designation-for-mdma-assisted-psychotherapy-for-ptsd-agrees-on-special-protocol-assessment-for-phase-3-trials/
(9) FDA News Release. (2023, 23 Jun). FDA Issues First Draft Guidance on Clinical Trials with Psychedelic Drugs. FDA Issues First Draft Guidance on Clinical Trials with Psychedelic Drugs | FDA

4 RECENT STUDIES PERFORMED AT MAC CLINICAL RESEARCH

In recent years there have been 14 Phase I, Ib, and IIa clinical trials conducted at MAC Clinical Research involving psychedelics as the investigational medicinal product (IMP).

Drug types have included synthetic psilocybin, MDMA, synthetic arylcyclohexylamine (related to ketamine) and DMT, with therapeutic areas including Therapy-Resistant Depression, Anxiety and Major Depressive Disorder.

5 WHAT ARE THE UNIQUE CHALLENGES DATA MANAGERS FACE IN PSYCHEDELIC STUDIES

There are two main aspects of psychedelic studies that pose a challenge for data management: **questionnaires** and **evolving guidance** on the collection of psychedelic effects as adverse events.

QUESTIONNAIRES:

In the 14 psychedelic studies conducted at MAC Clinical Research, a total of 34 separate questionnaire types have been used.

Frequently Used Questionnaires	
Mystical Experience Questionnaire **(MEQ30)**	Montgomery and Asberg Depression Rating Scale **(MADRS)**
Columbia-Suicide Severity Rating Scale **(C-SSRS)**	Psychiatric Assessment **(MINI Interview 7.0.2)**

With so many questionnaire types, a key challenge is study set-up. Within the EDC system, the Data Manager must ensure:

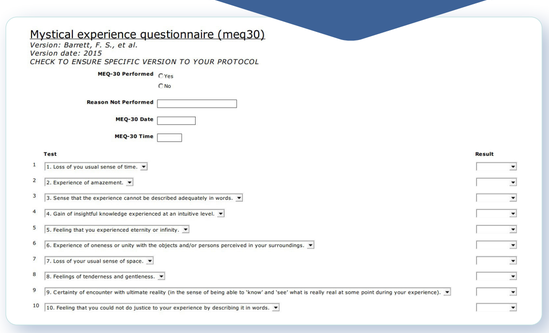
- Exact mapping of the questionnaire items
- Correct version of each validated, licenced questionnaire is adhered to with no deviation from the item text
- Form rules and validation checks are applied appropriately to aid entry, while being mindful that questionnaire entry may not be perfect

This can prove challenging as questionnaires are typically paper-based, with a layout that does not always translate to the eCRF.

During study conduct, Data Managers must take a different approach to data cleaning with acceptance of imperfect data. For self-reported questionnaires, queries against source are unlikely to resolve issues. With ePRO, queries are likely impossible and missing data is common. For the highest quality self-reported questionnaire data, completion should be performed on site or via telephone with a trained member of staff asking the questions.

MEQ30:

The MEQ30 is a particularly useful self-reported questionnaire for evaluating psychedelic effects. Administration is after a psychedelic dosing session. It consists of 30 items (such as 'Loss of your usual sense of time' and 'Loss of your usual sense of where you were') that rate the degree to which the subject experienced various phenomena during a psychedelic session.


Mystical experience questionnaire (meq30)
Version: Barrett, F. S., et al.
Version date: 2015
CHECK TO ENSURE SPECIFIC VERSION TO YOUR PROTOCOL

MEQ-30 Performed ○ Yes ○ No
Reason Not Performed
MEQ-30 Date
MEQ-30 Time

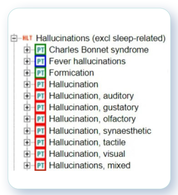
	Test	Result
1	1. Loss of you usual sense of time.	
2	2. Experience of amazement.	
3	3. Sense that the experience cannot be described adequately in words.	
4	4. Gain of insightful knowledge experienced at an intuitive level.	
5	5. Feeling that you experienced eternity or infinity.	
6	6. Experience of oneness or unity with the objects and/or persons perceived in your surroundings.	
7	7. Loss of your usual sense of space.	
8	8. Feelings of tenderness and gentleness.	
9	9. Certainty of encounter with ultimate reality (in the sense of being able to 'know' and 'see' what is really real at some point during your experience).	
10	10. Feeling that you could not do justice to your experience by describing it in words.	

EVOLVING GUIDANCE FROM REGULATORY BODIES AND THE IMPACT OF ADVERSE EVENT RECORDING:

Recent draft guidance advises that all adverse events including psychedelic effects, should be recorded for psychedelic trials[8]. At MAC Clinical Research, Data Management has proactively worked with coding specialists and Principal Investigators to consider how best to record these effects previously recorded on questionnaires.

Consistency and accuracy of the AE verbatim term for psychedelic effects are important. Guidance includes:

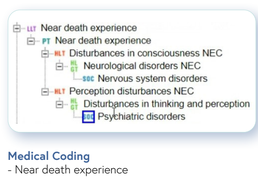
- AE symptoms need to be captured consistently per the Diagnostic and Statistical Manual of Mental Disorders (DSM) classifications, where possible
- Terms such as 'feels like' should be avoided
- Higher Level Terms (HLT) of Hallucination' or 'Perception Disturbances' should specify the type for the Preferred Terms (PT), e.g.
  - 'Hallucination, visual'
  - 'Perception disturbance – near death experience'
  - 'Perception disturbance – time perception altered'
- Terms should not be too specific (e.g. 'Hallucinations, visual – saw an animal in the room')
- Each type of Hallucination or Perception Disturbance should be recorded separately


HLT Hallucinations (excl sleep-related)
PT Charles Bonnet syndrome
PT Fever hallucinations
PT Formication
PT Hallucination
PT Hallucination, auditory
PT Hallucination, gustatory
PT Hallucination, olfactory
PT Hallucination, synaesthetic
PT Hallucination, tactile
PT Hallucination, visual
PT Hallucinations, mixed

Medical Coding
- Hallucinations


HLT Perception disturbances NEC
PT Autoscopy
PT Deja vu
PT Delusional perception
PT Derealisation
PT Flashback
PT Illusion
PT Imperception
PT Jamais vu
PT Near death experience
LLT Near death experience
PT Phantom vibration syndrome
PT Pseudohallucination
PT Time perception altered

Medical Coding
- Perception disturbances


LLT Near death experience
PT Near death experience
HLT Disturbances in consciousness NEC
SOC Neurological disorders NEC
SOC Nervous system disorders
HLT Perception disturbances NEC
SOC Disturbances in thinking and perception
SOC Psychiatric disorders

Medical Coding
- Near death experience

During study set-up, where this draft guidance is to be followed, it is worthwhile considering the expected psychedelic effects based on the receptor action. Verbatim terms may be listed and where these do not autoencode in the MedDRA dictionary, the Data Manager may request updates for the next version.

Lastly, during study conduct the AEs and questionnaire reported psychedelic effects need to be cross-checked by the Data Manager to ensure a match for the type of effect and the date/time.

6 THERAPEUTIC AND PATIENT SAFETY CONSIDERATIONS

For the safety of participants, the dosing rooms at MAC Clinical Research contain video monitoring and audio capture equipment. During dosing sessions, the subject is monitored by a Dosing Session Monitor or an in-room delegate. This monitoring may be performed in the room and/or through continuous monitoring of the audio/visual capture. These recordings are reviewed for any personally identifiable information and where the sponsor requests the recordings be provided to them at the end of a study, the recording is anonymised.

7 CONCLUSION

The positive impact psychedelics can have on mental health was evident more than half a century ago. Regrettably, research into their benefits was delayed for more than a generation by a political 'war on drugs'. The renewed interest in their use for mental health disorders is leading to an ever-increasing number of clinical trials and the captue of vast quantities of questionnaire data. With recent regulatory guidance stating psychedelic effects previously documented on such questionnaires are now captured as adverse events, there is a need to ensure this data is accurate, meaningful and can be used for analysis.