The concept of the Yale University Open Data Access (YODA) project (1) has been described previously (2). ~~We write to share our experience using it and the potential applications for research in clinical psychopharmacology, as we believe it is an under-utilized resource.~~

Large amounts of data are collected during clinical trials, and although summary outcomes are reported in publications, the datasets themselves are infrequently shared. The YODA Project was developed in 2013 to promote and facilitate the responsible sharing of clinical trial data. Data partners are both commercial (e.g. Johnson & Johnson, Medtronic) and academic (Queen Mary University Hospital) and provide access to large quantities of participant-level data from clinical trials, including case report forms, clinical study reports and protocols (2). The trials available through the YODA project are conducted in a range of conditions including: Alzheimer's disease, attention deficit hyperactivity disorder, bipolar affective disorder, depression, cancer, epilepsy, HIV, inflammatory conditions, and schizophrenia. Most trials are conducted in adults, but harder to reach groups such as children and older adults with dementia are also available.

We write to share our experience using it and the potential applications for research in clinical psychopharmacology, as we believe it is an under-utilized resource. In the field of psychiatry, only fifteen studies have been published, based on analysis of data available on YODA. In these studies, YODA data has primarily been used to address secondary research questions, through re-analysis of trial data and pooling of participant and study level data in meta-analyses (3, 4).

Data use is granted to prospective researchers following formal request and an outline of the proposed analysis. Once agreed, data are accessible via a remote desktop to a secure online platform. Programs available within the platform include: R and RStudio, Stata, Anaconda, Spyder, JAGS, and a suite of OpenOffice programs. If different analytical tools are required the YODA team will consider if they can be made available. It is not possible to access the internet through the platform and no participant-level data can be removed from

the platform. To export files, such as result tables and figures, approval needs to be requested.

We summarize in Table 1 the studies available in YODA pertinent to psychopharmacology. The majority of studies are randomised double blind controlled trials that are placebo controlled or parallel studies comparing medication, but data from open label trials are also available. Importantly, some of the available data is from trials that were not published.

We were granted access to two studies that contained pharmacokinetic data on risperidone from placebo controlled studies in people with dementia and psychosis or aggression (NCT00253123 and NCT00249145), with a combined total enrolment of 1021 participants. The purpose of our analysis was to replicate the findings of a previously published pharmacokinetic model for risperidone and the active metabolite 9-hydroxy (OH)-risperidone in patients with dementia (5).

Through the YODA project we were able to access the trial protocols, case report forms, clinical study reports and a data file dictionary. Approximately thirty data files were supplied with each trial including: subject characteristics (e.g. age, sex, height, weight, psychiatric diagnosis), trial medication administration, adverse event logs, concomitant medication and ~~diseases~~diagnoses, laboratory results (e.g. serum creatinine), ECG findings (e.g. QTc), pharmacokinetics (e.g. risperidone and metabolite plasma concentration), physical examination findings, vital sign measurements, symptom rating scales (e.g. Behavioral Pathology in Alzheimer's Disease, Cohen-Mansfield Agitation Inventory), cognition and functioning (e.g. Mini-Mental State Examination, Functional Assessment Staging Tool), and side-effects (e.g. Extrapyramidal Symptom Rating Scale).

Without access to this data, in order to conduct our study, we would have been required to design and conduct a separate pharmacokinetic study, which would likely not be feasible due to the resources required. The data allowed our group to replicate our previous finding that age was associated with a significant reduction in risperidone clearance; and that at

least 20% of patients with dementia had high concentration to dose ratios of the active moiety (summed concentrations of risperidone and 9-OH-risperidone) and would be described as 'functionally poor metabolisers' (6). These findings are important, as they argue for the use of therapeutic drug monitoring early in treatment, to avoid dose escalation in those at greatest risk of excessive drug exposure and strengthens the recommendation for risperidone dosing in dementia to be guided by age (5).

Noteworthy limitations of the YODA platform included data missingness. In one trial (NCT00249145) medication administration times were not included, rendering data on plasma concentration largely un-useable. Additional information was requested through the YODA project but was not available as the trial was conducted in 1995. In a second trial, administration and sampling times were reported for 142 of the 178 plasma samples. Researchers also need to be aware of the limited range of programs available within the secure platform, as this can create additional challenges. It was not possible to access the modelling software most commonly used (NONMEM and Monolix) and so we adapted our approach to model development tools within R. Accessing and conducting analyses within the secure platform could be slow at times.

It should be noted that alternative data sharing systems are available e.g. ClinicalStudyDataRequest (7), whose data partners include GSK and Novartis and Vivli (8), whose partners include AstraZeneca and Pfizer. We do not have experience with these other platforms although they are described to function in a similar manner to the YODA project i.e. requiring formal request and access to data via a secure platform. An additional benefit of these platforms with multiple data partners is they may allow combined analyses of data from multiple different trials.

In summary, the YODA platform is a free and extensive source of trial data (both published and unpublished), which can be used to carry out meta-analysis, or to analyse individual level data. The range of trial data available has potentially wide applications for clinical psychopharmacology research e.g. analyses of response to treatment, side-effects,

physiologic changes and pharmacokinetics. Researchers who are interested~~ing~~ in utilising YODA need to establish whether the specific data of interest are available and that the planned analysis can be conducted using YODA approved programs.

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Conflict of Interest and Disclosure Statement

The authors report no conflict of interests.

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Table 1 – Summary of studies available within the YODA project, allied to psychopharmacology

Drug or therapy name	**Conditions**	**Number of studies**	**Enrolment range**	**Pharmacokinetic data availability**
Esketamine	Depression	13	30 – 802	Yes
Galantamine	Alzheimer's disease	20	130 – 2051	Yes
Methylphenidate	Attention deficit hyperactivity disorder	12	78 – 1323	Yes
Paliperidone (including Long Acting Injection)	Schizophrenia, Bipolar affective disorder	44	5 – 1812	Yes
Risperidone (including Long Acting Injection)	Schizophrenia, Bipolar affective disorder, Depression, Dementia, Autism, Conduct disorder	59	13 – 753	Yes*
Topiramate	Bipolar affective disorder, Alcohol dependence, Binge eating disorder	8	13 – 434	Yes**
Graded Exercise Therapy	Chronic fatigue syndrome / myalgic encephalomyelitis	1	211	Not applicable

* No pharmacokinetic data availability described in Clinical Study Report Synopses for depression trials

** No pharmacokinetic data availability described in Clinical Study Report Synopses for bipolar affective disorder or binge eating disorder trials