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Short communication

An assessment of the utilization of the preclinical rodent model literature in clinical trials of putative therapeutics for the treatment of alcohol use disorders

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ABSTRACT

Objective: Rodent models of Alcohol Use Disorders (AUD) are used extensively by preclinical researchers to develop new therapeutics for the treatment of AUD. Although these models play an important role in the development of novel, targeted therapeutics, their role in bringing therapeutics to clinical trials is unclear, as off-label use of existing medications not approved for the treatment of AUD is commonly seen in the clinic and clinical trials.

Method: In the current study, we used the Clinicaltrials.gov database to obtain a list of drugs that have been tested for efficacy in a clinical trial between 1997 and 2017. We then conducted a set of literature searches to determine which of the 98 unique drugs we identified had shown efficacy in a rodent model of an AUD prior to being tested in a clinical trial.

Results: We found that slightly less than half of the drugs tested in clinical trials (48%) had shown prior efficacy in any rodent model of an AUD, while the remaining 52% of drugs were used off-label, or in some cases, following non-published studies.

Conclusion: This study raises the question of how clinical researchers incorporate results from preclinical studies in the decision to bring a drug to a clinical trial. Our results underscore the need for ongoing communication among preclinical and clinical researchers.

1. Introduction

The traditional view of the therapeutic development process begins with preclinical models of a human disease and ends with the success or failure of the drug in Phase II clinical trials. However, off-label use of approved medications is a common practice in the clinic and in clinical trials (O'Brien et al., 2017). Thus, though a drug may be indicated to treat a particular disorder, it is common for providers to prescribe the drug to treat a condition with similar symptoms. For some diseases, such as different types of cancers, preclinical rodent models are heavily relied upon during preclinical development, and have led to many pharmaceuticals still being used today (Day et al., 2015). However, the role that preclinical models play in developing therapeutics may not be consistent for all disorders (O'Brien et al., 2014).

The average cost of developing a drug approved by the US Food and Drug Administration (FDA) ranges from $0.5 billion-2.0 billion and takes an average of twelve years to complete all stages of the approval process (Adams and Brantner, 2006). Despite showing efficacy in preclinical testing, many drugs will still fail in Phase II and III clinical trials (Day et al., 2015). Approximately three-quarters of the drugs that fail after Phase II can be attributed to efficacy or safety issues (Arrowsmith and Miller, 2013). These failures may be the result of a number of inadequacies in the drug development process, including the preclinical models used. However, preclinical testing costs considerably less than clinical trials (Adams and Brantner, 2006), and can determine if clinical trials should be pursued.

The present study examines the use of preclinical rodent models of Alcohol Use Disorders (AUD) in the decision to test a putative AUD therapeutic in a clinical trial. AUD are characterized by a pattern of alcohol use leading to impairment or distress, which can include drinking larger quantities over a longer time than intended, craving, continued drinking despite negative consequences caused by alcohol consumption, tolerance, and physiologic withdrawal (American Psychiatric Association, 2013). Due to the heterogeneity of the disorders, overlap with other drug abuse disorders, numerous therapeutic targets, and overlapping symptomatology with other disorders (Clapp, 2012; Egli, 2005), it is difficult to determine which aspects of AUD are most relevant to model. Numerous models of voluntary ethanol intake

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Table 1
Comparison of the first instance of each drug in a preclinical and clinic study of AUD. For a complete description of the table, refer to the Results section. The three columns immediately to the right of the drug name include the dates that the drug was first studied in a clinical trial, a rodent intake model of AUD, and a rodent model of AUD other than an intake model, respectively. If there is no date indicated in the fourth column, we did not find any published evidence of the drug being studied in a rodent intake model of AUD. If no date is present in the fifth column indicating any rodent model of AUD excluding intake models, there was either no other preclinical model that preceded the date of the first intake study or, the date of the study using an intake model preceded the date of the clinical trial. Finally, the three leftmost columns contain citations for dates listed in the table. If no citation is provided for the date of the first clinical trial, that date was taken from the NIH Clinicaltrials.gov database. If there is a citation for the first clinical trial, that study was found in PubMed using the search terms described in Methods.

Drug Name	Therapeutic Category	Earliest Date in Clinical Trials	Earliest date in rodent intake model	Earliest date in any rodent alcohol model (excluding intake models)	Intake Model Citation	Clinical Trial Citation	Rodent Model Citation (any behavior other than intake)
Dutasteride (Avodart)	5α-reductase Inhibitor	Apr-06	–	–	–	–	–
Dexmedetomidine (Precedex)	α-adrenergic Agonist	Sep-09	–	Aug-97	–	–	(Riihioja et al., 1997)
Guanfacine (Tenex, Intuniv)		Apr-06	1986	–	(Parale and Kulkarni, 1986)	–	–
Doxazosin (Cardura)	α-adrenergic Antagonist	Nov-11	Feb-13	–	(O'Neil et al., 2013)	–	–
Mirtazapine (Remeron)		Apr-04	–	Aug-16	–	–	(Arora and Vohora, 2016)
Prazosin (Minipress)		Apr-04	Mar-08	Sep-83	(Walker et al., 2008)	–	(Trzaskowska and Kostowski, 1983)
Yohimbine		Jan-08	Jul-87	–	(Andronova, 1987)	–	–
Disulfiram (Antabuse)	Aldehyde Dehydrogenase Inhibitor	Sep-49	Jan-66	–	(Schlesinger, 1966)	(Glud, 1949)	–
Sulfasalazine (Azulfidine)	Aminosalicyclic Acid Derivative	Mar-10	Oct-2016	–	(Truitt et al., 2016)	–	–
Perampanel (Fycompa)	AMPA Receptor Antagonist	Apr-15	–	–	–	–	–
D-Cycloserine	Antibiotic	Nov-97	May-09	Nov-08	(Groblewski et al., 2009)	–	(Vengeliene et al., 2008)
Minocycline (minocin)		Jul-15	Jun-11	–	(Agrawal et al., 2011)	–	–
Carisbamate	Anticonvulsant, miscellaneous	Feb-13	Aug-09	–	(Rezvani et al., 2009)	–	–
Divalproex (Depakote, sodium valproate, valproic acid)		Mar-80	Dec-98	Oct-75	(Gardell et al., 1998)	(Boeckh, 1980)	(Hillbom, 1975)
Gabapentin (Neurontin, Gralise)		Jul-01	–	Oct-97	–	–	(Watson et al., 1997)
Gabapentin enacarbil (Horizant)		Jul-15	–	–	–	–	–
Lamotrigine (Lamictal)		Feb-10	Jan-13	Dec-07	(Vengeliene et al., 2013)	–	(Vengeliene et al., 2007)
Levetiracetam (Keppra)		Mar-04	Feb-11	–	(Zalewska-Kaszubska et al., 2011)	–	–
Pregabalin (Lyrica)		Jul-09	–	Jul-06	–	–	(Becker et al., 2006)
Topiramate (Topamax)		Sep-03	Jan-05	Jan-04	(Gabriel and Cunningham, 2005)	–	(Cagetti et al., 2004)
Vigabatrin (Sabril)		Jan-96	Sep-93	–	(Wegelius et al., 1993)	(Stuppaeck et al., 1996)	–
Zonisamide (Zonegran)		Jul-06	May-07	–	(Knapp et al., 2007)	–	–
Flumazenil (romazicon)	Antidote	1993	Jan-84	–	(Beaman et al., 1984)	(Nutt et al., 1993)	–
N-acetylcysteine		Dec-07	–	May-15	–	–	(Schneider et al., 2015)
Ivermectin (Stromectol, Soolantra, Sklice)	Antihelminthic	Feb-14	Jun-11	–	(Kosten, 2011)	–	–
Fenofibrate	Antilipemic	May-14	Nov-14	–	(Ferguson et al., 2014)	–	–
Aripiprazole (Abilify)	Atypical Antipsychotics	Apr-04	Jul-06	–	(Ingman et al., 2006)	–	–
Olanzapine (Zyprexa)		Sep-02	Mar-06	–	(Ingman and Korpi, 2006)	–	–
Quetiapine (Seroquel)		Nov-02	–	Mar-11	–	–	(Celikyurt et al., 2011)
Risperidone (Risperdal)		Sep-05	1993	–	(Panocka et al., 1993)	–	–
Ziprasidone (Geodon)		Oct-04	–	Mar-11	–	–	(Celikyurt et al., 2011)
Propranolol (Inderal, Hemangeol, Innopran)	β-adrenergic Antagonist	Aug-75	1974	–	(Begleiter, 1974)	(Zilm et al., 1975)	–
Phenobarbital (Luminal)	Barbiturate	Aug-87	May-75	–	(Rondeau and Jolicoeur, 1975)	(Young et al., 1987)	–
Thiopental (Pentothal)		Nov-05	–	Nov-92	–	–	(Gil et al., 1992)

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