



## University of Dundee

### What matters is more than just the choice of pharmaceutical agent

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### WHAT MATTERS IS MORE THAN JUST THE CHOICE OF PHARMACEUTICAL AGENT

*Any model to guide the choice of agonist substitute drugs for substance misusers must reflect the heterogeneity of the treatment population as well as the pharmacodynamics and pharmacokinetics of the proposed agents. Even in the face of compelling evidence of clinical effectiveness, as is seen in the case of opioid replacement, the stigmatization of substance misusers by society reduces drug development and consequently the availability of valuable substitution therapies.*

Darke & Farrell propose a framework to determine the suitability of agonist maintenance as a treatment option for problems involving the main classes of psychoactive drug [1]. They conclude that there is a strong case for agonist maintenance in opioid dependency—especially in the case of long-acting drugs that match closely the authors' framework. They also propose that there is a place for substitution treatment in nicotine dependency. Their framework does not, however, support a maintenance role in the other drug classes.

The model proposed would be enhanced by consideration of additional key variables which may influence clinical outcomes. The pharmacokinetics and pharmacodynamics of drugs are important factors, differing greatly for the same medication given orally, as long-acting depot or as intravenous injection. Clearly, the neuropharmacological effects and subjective experience of taking such medications are affected not only by the drug chosen (and its mechanism of action), but also by the way it is taken. Some agents/routes of ingestion will give rapid and pronounced initial effects which some patients will value as approximating to their experiences with their chosen drug of misuse. Others will have less rapid initial peak effects, but deliver a more protracted clinical effect. This will influence suitability as a substitution agent.

Also, the clinical value of these treatments reflects individual patient circumstances and context. Substance misusers are a heterogeneous group, often having complex drug histories and comorbid psychological difficulties, in challenging social circumstances. Matching an individual to a specific drug must take this into account. Indeed, as an individual responds to treatment the clinical approach, as well as preferred agent to meet their clinical circumstances, may change. As a result there are some agents available for opioid dependency which meet the proposed criteria less fully but may still be clinically valuable in specific circumstances. Diamorphine, for example, has developed an evidence base demonstrating clinical effectiveness in specific circumstances which mitigates against their lack of a 'match' to the proposed model [2]. This model must be modified to reflect these variables more clearly.

Unfortunately, even in the case of opioids, the menu of agents available remains limited. A paucity of drug development since methadone reached prominence as a substitution agent has limited the ability to refine treatments to match patient need. In the United Kingdom, only one new opioid substitution therapy (OST) has become licensed for use in the last 20 years, despite the extent and consequences of opioid dependency. Systematic reviews have consistently shown OST to be highly cost-effective [3], but this has not increased drug development activity in the pharmaceutical industry. This reluctance may reflect society's stigmatisation of the substance misuse population [4]. The use of OST is constantly challenged politically and through the media [4,5]. This cultural opposition to substitution therapy—even when treatments meet objective criteria as appropriate agonist agents and enjoy a strong evidence base for harm reduction—suggests that we have not yet won the battle in the public

debate regarding the benefits of this treatment approach. An unhelpful polarity exists between (mainly psychosocial) interventions, targeting immediate abstinence and pharmacological substitution treatments, promoting stabilization and harm reduction. In reality, both are required to tackle this complex biopsychosocial condition, and better research into whole treatment systems combining both approaches is required [6,7]. This situation also results in limited availability of treatment options to address clinical challenges. If more opportunity for development of useful agents was offered, the field could move on to address specific criticisms, such as the lack of strong evidence for achieving more ambitious recovery outcomes or the limited treatments available to meet individuals' needs.

Finally, it must be recognized that potential cases exist for agonist prescribing in other drug classes—for example, benzodiazepines [8] or amphetamines [9]. No such agents currently meet the proposed criteria, but some are nevertheless being used pragmatically in clinical practice despite a lack of evidence to support this. This is not unlike the clinical circumstances that saw the genesis of OST in the face of HIV. Here again, there is a need for programmes of clinical research to explore more effectively the potential benefits of these treatments.

The proposed framework [1] is a helpful first step when considering potential pharmaceutical treatments for substance misuse, but the model addresses only part of the story. Clinicians will continue to be faced with people who put themselves at risk and for whom current evidence-based interventions do not help. More high-quality research is needed reflecting the heterogeneity of the substance misusing population. Even when the clinical evidence base is compelling, cultural/socio-political issues still drive stigma and a reluctance to progress this type of clinical care. It is important that clinicians and scientists continue to articulate clearly the complexity of this population, as well as the evidence that we can reduce significantly the negative impacts of illicit substance use.

#### Declaration of interests

In the last 10 years B.K. has received pharmaceutical industry funding for specific activities, including the following: meetings/educational input—a single honorarium from Lundbeck Pharmaceuticals—for organizing, chairing and presenting an educational seminar, Spring 2014; a single honorarium from Britannia Pharmaceuticals for meeting as a member of an advisory board, August 2015; research income—a research grant from Indivior, 2015/6. A research project is being planned by Braeburn Pharmaceuticals: this is planned to commence in 2016 and may result in funding to the local NHS service based

on recruitment and activity. There are no additional financial or other relevant links to companies with an interest in the topic of this article. E.D. is a principal investigator in two ongoing trials of relapse prevention medication where the research is being funded by the National Institute for Health Research (NIHR), but the medication is being supplied by Merck (Acamprosate) and iGen (Naltrexone implant). There are no financial or other relevant links to companies with an interest in the topic of this article. J.S. and his employer (King's College London) have received, connected to his work, project grant support and/or honoraria and/or consultancy payments from Department of Health, NTA (National Treatment Agency), PHE (Public Health England), Home Office, NICE (National Institute for Health and Clinical Excellence) and EMCDDA (European Monitoring Centre for Drugs and Drug Addiction), as well as research grants from (last 3 years) NIHR (National Institute on Health Research), MRC (Medical Research Council) and Pilgrim Trust. He has worked with WHO (World Health Organization), UNODC (United Nations Office on Drugs and Crime), EMCDDA, FDA (US Food and Drug Administration), NIDA (US National Institute on Drug Abuse) and with other international government agencies. His employer (King's College London) has also received, connected to his work, research grant support and/or payment of honoraria, consultancy payments and/or travelling and/or accommodation and/or conference expenses from pharmaceutical companies (including, past 3 years, Martindale, Reckitt-Benckiser, MundiPharma, Braeburn/MedPace), trial medication supply from iGen, and also discussions with Alkermes, Fidelity International, Rusan, Titan, Indivior, Adapt and Camurus concerning medicinal products potentially applicable in the treatment of addictions and related problems, and has argued for the development of improved formulations. This includes exploration of the potential for, and consideration of research trials of, improved medications with less abuse liability, longer duration of action (e.g. implant or depot formulations) and also novel non-injectable emergency medications. For updated information see John Strang's information on the Departmental website at: <http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx>

**Keywords** Context, patient experience, stigma, substitution therapy, treatment choice.

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## RESPONSE TO COMMENTARIES ON ‘WHICH MEDICATIONS ARE SUITABLE FOR AGONIST DRUG MAINTENANCE’

*As the commentators note, treatment refractory substance use disorders are a clinical reality, and pharmacological intervention is, for many patients, a clinical necessity. Criteria to define what constitutes an appropriate agonist are essential. We are gratified that the commentators found this to be ‘a helpful first step’ in this endeavour.*

We thank the commentators for their considered comments on our For Debate piece addressing agonist maintenance [1]. In our opinion, the For Debate series provides a valuable platform for open discussion of clinical issues without the constraints of a formal comprehensive review. It is our hope that this piece, and the associated commentaries, do indeed encourage debate and research in this crucial field. It should be noted that the issue of maintenance is not unique to this field, but also applies to medications such as antidepressants. We value clear recognition, and understanding, of a patient

population that requires sustained medication for their chronic condition.

Kidd and colleagues [2] describe the work as ‘a helpful first step’, which is exactly what we intended. Our aim was not to be prescriptive, but to engender further discourse on the role of maintenance across substances. As noted by Lingford-Hughes [3], long-term maintenance is not employed widely outside the opioids and, to a lesser extent, nicotine. Furthermore, as Kidd and colleagues [2] note, even within opioids the agonist treatment palette remains limited. The clinical reality is that, as argued by Shoptaw [4] and Walter & Soyka [5], abstinence is not always a feasible treatment goal. Treatment-refractory substance use disorders are a clinical reality, and pharmacological intervention is, for many patients, a clinical necessity [6].

Not all drugs appear appropriate for agonist maintenance and, as we have argued, the characteristics of some drug classes may well preclude maintenance. Only research will tell. Cannabis and the benzodiazepines, however, appear ripe for such work, but we must have criteria to define our understanding of what constitutes an appropriate maintenance agonist. There are a plethora of issues to be examined, many of which are raised in the commentaries, that includes a better understating of drugs and brain chemistry, pharmacokinetics, pharmacodynamics and route of administration. We look forward to the debate, and to new research advancing our treatment options. We do hope all this contributes to the development of new treatment agents which show demonstrable treatment benefit and help us to move forward in the development of addiction treatment technology.

## Declaration of interests

None.

**Keywords** Alcohol, benzodiazepines, cannabis, maintenance, nicotine, opioids, psychostimulants.

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