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Commentary: Disulfiram and the Zenalyser®: Teaching an Old Dog New Tricks

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ABSTRACT

The principal purpose of this Commentary is for one of the key developers to describe a recent innovative device that has the potential to improve the treatment of alcohol dependence. The Commentary initially surveys the current place of disulfiram in the treatment of alcohol dependence, looking back at its historical reputation as an ineffective and potentially dangerous medicine. Methodological problems in disulfiram research are briefly mentioned, and more recent research is described that shows disulfiram to be more effective than naltrexone or acamprosate and effectively corrects its inaccurate historical reputation. The article describes an innovative device, a hand held, dual sensor breathalyser called a Zenalyser®, which measures both alcohol levels and disulfiram metabolites on a sample of breath. The way the Zenalyser® can be used in clinic or remotely is explained. Common problematic areas for alcohol treatment services are commented upon, together with the potential of the Zenalyser® to improve disulfiram treatment outcomes, reduce treatment costs and decrease workload in overstretched services.

Commentary: "Disulfiram: Teaching an Old Dog new Tricks"

Innovations in the addictions field which have the potential to improve outcomes, reduce costs and decrease workload all at once do not come along very often. This is especially so if the innovation is easy to use and fairly low cost. I reported in 2015 on the development of a hand-held device, the Zenalyser®, which, for patients with the common disorder of alcohol dependence, could hit the nail on the head. Advances in medicine do not necessarily come from highly expensive developments - simply tweaking established treatments can result in significant improvements both for patients and for treatment services.

What are the challenges in the alcohol dependence field? In the UK they amount to overwhelmed services with long waiting lists, brief treatments and high relapse rates. The staple of treatment is some form of counselling, with medication only being offered to those fortunate enough to get to see a medical professional who may have little specialist knowledge.

There are few medications to offer people with alcohol dependence. The most commonly used are naltrexone and acamprosate, with disulfiram coming a distant third. However, disulfiram has the capacity to maintain abstinence rather than

merely reduce craving, and if necessary, can be combined with naltrexone or acamprosate. So why is disulfiram so badly neglected?

Firstly, research in the 1980s found little improvement in patients using disulfiram. Why? Principally because they didn't take it. I remember as a trainee psychiatrist being told prescribing disulfiram was a complete waste of time. That sort of message sticks, and it certainly became widely accepted in the UK.

Secondly, disulfiram had a reputation for being dangerous. It could kill you if you drank on top of it. That's another message that sticks and is difficult to dislodge. But dislodged it should be, because in recommended dosages (much lower than dosages used in the first 40 years of disulfiram prescribing) it is safe, providing that the major contraindications (psychosis, pregnancy, serious cardiovascular disease, hypertension, stroke – all of which are relative contraindications and not absolute) are attended to. Disulfiram, in fact, has fewer side effects than aspirin[1].

Thirdly, randomised placebo controlled trials found little or no difference between disulfiram and placebo. In these days of evidence based medicine this is a killer, of course. However, disulfiram works by producing the *threat* of a highly unpleasant reaction if alcohol is consumed. A patient taking a placebo experiences the same potential threat. Think of speed cameras on the roads. Do they have film in or not? You don't know, so you will drive carefully anyway. That is the problem with placebo controlled trails of disulfiram. When alternative medicines like naltrexone and acamprosate are (wrongly) perceived to be more effective and much safer, disulfiram is put on the back burner.

Is the case for disulfiram hopeless? Thankfully not. The first problem of poor compliance has been addressed by regularly supervising the consumption of disulfiram, usually by a spouse or partner, but occasionally by a pharmacist. Skinner et al's meta-analysis[2] measured the "effect size" of disulfiram when either unsupervised or supervised. Using Hedge's g scale (0.2-0.3 small effect, 0.5 medium effect, 0.8 large effect) unsupervised disulfiram had an effect size of 0.1, which fits perfectly with previous research. However, supervised disulfiram had a large effect size of 0.82. Many other studies confirm this finding.

What about the competition from naltrexone and acamprosate? Skinner et al[2] found disulfiram had an effect size over naltrexone of 0.76, and an effect size over acamprosate of 0.77. Put simply, disulfiram produces fairly large improvements in treatment outcomes compared to naltrexone or acamprosate. This finding supports other research, such as that of the Swedish Technology Assessment[3] of effect sizes (naltrexone 0.25, acamprosate 0.25, disulfiram 0.5) and Da Sousa's findings[4,5] of 12 month abstinence rates (naltrexone 44% vs disulfiram 86%; acamprosate 46% vs disulfiram 88%).

The case for supervised disulfiram is, therefore, quite strong. Supervision can overcome the problem of poor compliance. It is safe in recommended dosages when used in appropriate patients. Taking account of methodological problems in research trials it proves to be quite powerfully effective and is superior to both naltrexone and acamprosate. The outstanding results of the OLITA programme[6] which, using supervised disulfiram, produced non-relapse rates of 52% and total abstinence rates of 26% over 9 years in severely alcohol dependent subjects powerfully makes the point. All seems well and good.

When it comes to disulfiram then, why is any further innovation required? Well, things aren't quite what they seem. Supervision has its problems. In practise partners or spouses who supervise disulfiram are usually conscientious for the first 2 or 3 months, after which attentiveness often declines so compliance falls by the wayside and results in relapse. Relationships may break down. Craving patients have a way of pretending to take the disulfiram when they are not. Vomiting the disulfiram, or substituting it for a similar looking tablet are not unknown. Trips to the pharmacist for supervision have, unlike methadone for example, no reward and therefore stop. Some patients are difficult to supervise because they are highly mobile as a result of work and travel, or simply have no-one who will supervise them. Furthermore, the remarkable results of the OLITA programme were achieved not only with supervised disulfiram, but also with intensive support over a long period of time – not something which is transferrable to ordinary treatment services. Here is where the Zenalyser® can make a difference.

What is the Zenalyser®? It is a hand-held dual sensor breathalyser that detects both alcohol and the metabolites of disulfiram. The accuracy of the disulfiram metabolite photo-ionisation sensor has been compared against the gold standard Gas Spectroscopy Mass Chromatography technique with very high levels of agreement. The high level of accuracy of the fuel cell alcohol sensor is well known. If disulfiram is taken daily, the sensitivity and specificity of the Zenalyser® is 100%. The sensitivity drops to 80% if a measurement is taken 2 or 3 days after the last tablet has been taken, but the specificity remains 100%[7].

How is the Zenalyser® used? Usually a patient, often after an alcohol detoxification but certainly whilst abstaining, blows into the Zenalyser® to obtain baseline readings (which will be negative for alcohol and disulfiram metabolites). The Zenalyser® is simply connected to a computer, the patient blows into the device for about 10 seconds, and the readings are graphed and tabulated for

very simple interpretation. Then disulfiram is commenced on a daily basis, and over 2-3 days a therapeutic level will be reached. This corresponds to Zenalyser® readings of over 5 parts per million (ppm) for disulfiram metabolites and below 5 micrograms per 100mls of breath for alcohol (assuming the patient is still abstinent). Thereafter the patient takes disulfiram daily and provides regular Zenalyser® samples to the supporter (clinician or supervising partner). Alternatively the Zenalyser® can be used remotely (from anywhere in the world with an internet connection) for the patient to blow into and, using a simple app, send the results to the supporter on a daily basis.

In routine clinical practice patients in alcohol treatment services, having commenced disulfiram, should be reviewed for several weeks or months. Typically an optimal level of follow-up support is not available due to services being overstretched and under-resourced. Additional common problems are that patients may falsely report compliance with disulfiram during review or relapse rapidly and not attend for review at all.

How can the Zenalyser® help services like this? Firstly, compliance with disulfiram can now be quickly and objectively checked. Secondly, using the Zenalyser® remotely enables a patient to send daily readings to their supporter. Reducing levels of disulfiram metabolite, the appearance of alcohol, or failure to provide a reading can trigger immediate review to catch a relapse before it becomes established. Thirdly, remote monitoring means that the frequency of clinic review can be reduced to times of necessity rather than routine thus reducing workload and opening up clinic space. Fourthly, and importantly, each daily reading received from a patient remotely can be followed by a short email from the supporter feeding the results back and prompting them to continue to take their disulfiram tablet – thus providing daily support and monitoring in a quick and efficient way.

In summary, the Zenalyser® has the potential to deliver improved treatment outcomes, reduce costs and decrease workload. It is simple to use and fairly inexpensive. Early results with the Zenalyser® have been promising[8]. The device has now obtained European certification for non-remote use, with remote use pending. Costs for one instrument with a 5 year warranty are currently around $900, with small continuing costs for annual servicing and disposable mouth pieces. More information about the Zenalyser® can be found at www.zenamed.co.uk.

Conflict of interest

Keron D. Fletcher is a director of ZenaMed Ltd, the company producing the Zenalyser®.

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References

1. Gitlow SE. In: Eds: Gitlow SE and Peyser HS. **Alcoholism: a practical treatment guide**. New York. Grune and Stratton. 1980; p 273.
2. Skinner MD, Lahmek P, Pham H, et al. Disulfiram efficacy in the treatment of alcohol dependence: a meta-analysis. **Plos One.** 2014; Feb 10; 9(2): e87366.
3. Swedish Council on Technology Assessment in Health Care (**SBU**). Treatment of alcohol and drug abuse: an evidence-based review. **Int J Technol Assess Health Care.** 2002; Winter18(1):145-154.
4. De Sousa A, De Sousa A. A one-year pragmatic trial of naltrexone vs disulfiram in the treatment of alcohol dependence. **Alcohol and Alcoholism**. 2004; 39(6): 528-531.
5. De Sousa A. An open randomised study comparing disulfiram and acamprosate in the treatment of alcohol dependence. **Alcohol and Alcoholism.** 2005; 40(6): 545–548.
6. Krampe H, Stawicki S, Hoehe MR, et al. Outpatient Long-term Intensive Therapy for Alcoholics (OLITA): a successful biopsychosocial approach to the treatment of alcoholism. **Dialogues Clin Neurosci.** 2007; 9: 399–412.
7. Fletcher K, Stone E, Mohammad MW, et al. A breath test to assess compliance with disulfiram. Addiction**.** 2006 Dec; 101(12): 1705-10.
8. Fletcher K. Disulfiram and the Zenalyser: teaching an old dog new tricks. **Alcohol and Alcoholism**. 2015; pp1-2.