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

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Disulfiram is recommended by the National Institute for Health and Care Excellence as a cost effective drug for the treatment of alcohol dependence (NICE, 2011). Nevertheless, there continues to be suspicion regarding the usefulness of this medication, predominantly arising from the perception that compliance is poor. Several attempts to improve compliance have been made, the most notable of those being supervised consumption (e.g. Wright and Moore, 1990; Chick et al., 1992). Supervision is, however, not without its limitations—relationships break down, individuals are mobile, supervisors weary of their task.

The German Out-patient Long term Intensive Therapy for Alcoholics (OLITA) programme demonstrated that disulfiram can be extremely effective in maintaining abstinence from alcohol (Krampe et al., 2007). Over 50% of the 180 patients studied remained abstinent from alcohol for 9 years with high frequency support and long-term treatment. However, it is difficult to see how these key ingredients can be incorporated into services that are over-worked, under-resourced, and in locations distant from their patients.

In 2006 the author of this letter, together with colleagues, published the results of a study which demonstrated that the metabolic products of disulfiram can be identified on a sample of breath (Fletcher et al., 2006). The specificity and sensitivity of the technique are 100% if the patient is prescribed 200 mg disulfiram daily. Over subsequent years continuing work has brought this finding to the point of clinical application. By combining disulfiram and breath alcohol measurements in a small hand-held breathalyser and adding appropriate software, a device has now been manufactured that allows individuals prescribed disulfiram to be remotely supported and monitored on a daily basis from any geographical location with internet access.

In brief, this device, a Zenalyser®, works in the following way: a patient blows into the instrument, connects it to a computer and the result is exported to the treating team—a process that takes <45 s from start to finish. The treating team read the result and email the patient back, which takes no more than a couple of minutes depending on the content of the email. Alternatively, the Zenalyser can be kept at the treating base, and patients can attend at frequent intervals to provide breath samples.

Clinical observations (unpublished data) on ten severely alcohol-dependent patients followed up after in-patient detoxification for up to 3 years (mean = 11.3 months), have revealed very high disulfiram compliance rates, which is the main purpose of the technique. Nine out of 10 patients remained totally abstinent from alcohol. One cirrhotic female patient had two brief relapses of 1 week each during an 8-month period of daily support with the Zenalyser—this exceeded, by some considerable margin, her responses to treatment in the previous 30 years, despite three periods of residential rehabilitation.

There have been, however, a number of other benefits observed that were not anticipated and which go beyond improving disulfiram compliance rates. These are as follows:

- Relapse can be anticipated before it occurs, being inferred from rapidly falling disulfiram metabolite levels, the appearance of alcohol on the breath, or because the patient stops sending data.
- Out-patient follow-up no longer needs to be routine, but can be reserved for times of high risk thus reducing out-patient activity and other factors, e.g. travel time, carbon footprint.
- Daily support and monitoring can be provided together with encouragement, feedback, warnings, etc.—all of the components of good motivational enhancement—very rapidly, cheaply and with minimal staffing requirements.
- Patients can be supported and monitored on a daily basis even when they travel to foreign countries.
- Patients have been able to use Zenalyser data in legal situations, e.g. alcohol-dependent mothers involved in child protection cases; and doctors under medical supervision from their governing body.

Feedback from families and patients shows that they appreciate this technique, being reassured that when a patient leaves...
the safety of a detoxification or rehabilitation unit the clinical team continue with daily contact. Family members too, with permission, can read the emails from the treating team and be reassured that disulfiram has been taken and that the levels are in the therapeutic range.

There are limitations to the use of the instrument and to the conclusions that can be drawn at this stage. Home-based treatment with the Zenalyser currently requires patients to have daily access to a computer and the Internet. The technology needs to be developed to make use of smart phone communication. This would significantly widen accessibility to remote support and monitoring. Furthermore, the data upon which our observations have been based are restricted to a small group of severely dependent patients detoxified on our in-patient unit. No formal controlled trial has yet been undertaken but will be necessary to fully evaluate the potential of this novel technology.

Despite these limitations the clinical observations so far suggest that the Zenalyser has promise. It is now possible to provide high frequency support and long-term treatment (with minimal staffing requirements and at low cost). If these advantages of the OLITA programme can translate into over-worked and under-resourced clinical services, the Zenalyser will indeed have something to offer the busy clinician.

Conflict of interest statement. K.F. is Medical Director to ZenaMed Ltd, the company that invented and distributes the Zenalyser (www.zenamed.co.uk).

REFERENCES


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Marchiafava–Bignami Disease Presenting as Acute Dysarthria and Ataxia

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Dear editor,

This is a case of a 68-year-old right-handed man admitted to the hospital with 2 days of acute onset of slurred speech and unsteady gait. He denied any other neurological complaints. His past medical history was significant for alcohol dependence with daily alcohol use and 1 day a week of binge drinking for >10 years. He denied any history of alcohol-related seizures, DTs, psychiatric diagnosis or alcohol-related legal or interpersonal problems. The patient was oriented, able to name, read, repeat and follow commands. There was impaired short-term memory. He had severe dysarthria. Cranial nerves were intact. There was decreased vibration at toes with hyporeflexia at ankles; the remaining reflexes and motor exam were normal. There was dysmetria in all limbs and a wide-based ataxic gait. The differential diagnosis was a vascular event, alcohol-related cerebellar degeneration, Wernicke’s encephalopathy, Marchiafava–Bignami disease, paraneoplastic cerebellar degeneration or a posterior fossa mass. The baseline CBC and comprehensive metabolic panel were within normal limits except for an elevated white blood cell count and mildly elevated AST. Baseline vitamin levels were not obtained. The MRI-brain showed abnormal high DWI (diffusion-weighted imaging) and T2 signal in the splenium of the corpus callosum with no mass effect or edema and scattered T2 signal hyperintensities within the bilateral hemispheric white matter (Fig. 1). A diagnosis of Marchiafava–Bignami disease (MBD) was made. The patient was started on high-dose thiamine intravenously for 5 days (500 mg three times a day) and oral vitamin B complex. Seven days after the symptom onset there was significant improvement, the patient was able to ambulate unassisted and the dysarthria was improved. After discharge the patient was lost to follow-up.

MBD is known to be associated with chronic alcoholism and malnutrition. It used to be considered rare and fatal and diagnosed post mortem but imaging has allowed for early detection and intervention. It is characterized by demyelination and necrosis of the corpus callosum. Its pathogenesis is still unclear but it is attributed to deficiency of the B-complex group of vitamins (Bhat et al., 2014; Wenz et al., 2014).

The mean age of onset of MBD is 46 years. The most common manifestations are: cognitive impairment, dysarthria, disconnection syndromes, seizures and pyramidal tract symptoms (Heinrich et al., 2004). There are two acute/subacute types. Type A with major impairment of consciousness, seizures, dysarthria, hemiparesis and Type B presents dysarthria, gait disturbance, signs of interhemispheric disconnection and less impairment of consciousness. In Type A the entire corpus callosum is affected (100 vs. 10% in Type B) and more frequently presents with extracallosal lesions (47 vs. 17% in Type B). Type A has a worse prognosis (Heinrich et al., 2004). A chronic course has been described with progressive dementia, behavioral abnormalities and signs of interhemispheric disconnection (Menegon et al., 2005). The case presented was most likely Type B as there was no impairment of consciousness, only the splenium of the corpus callosum was affected and the prognosis was good.

The diagnosis is made with MR imaging of the brain, which shows lesions involving the central portion of the body of corpus callosum with sparing of dorsal and ventral layer. Lesions are hypointense on T1, hyperintense on T2/FLAIR showing diffusion restriction on DWI and variable reduction in ADC (apparent diffusion coefficient). The lesions lack contrast enhancement and do not show mass effect. In the chronic state, atrophy and cavitation of the corpus callosum is seen (Menegon et al., 2005; Kakkar et al., 2014).

There is no proven treatment. Folate, thiamine, vitamin B12 and other B vitamins are commonly used but the