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BNF Recommendations for the Treatment of Wernicke's Encephalopathy: Lost in Translation?

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We agree with Thomson and Marshall (2013) that the current prescribing of thiamine replacement therapy for Wernicke's Encephalopathy (WE) is ambiguous. In response to their article, we also advocate that any consensus on accurate thiamine treatment for WE should receive sufficient international attention, since too many patients with WE are currently inaccurately treated leading to unnecessary cases of Korsakoff's syndrome.

WE is a neurologic disease caused by thiamine (vitamin B1) deficiency. Most patients with WE have a background of chronic alcoholism and self-neglect (Sechi and Serra, 2007). Importantly, WE is also a life-threatening condition associated with a classic triad of acute neurological symptoms resembling delirium: confusion, ataxia and eye-movement disorders (McCormick *et al.*, 2011; Wijnia and Oudman, 2013). Usually, but not necessarily, patients will develop Korsakoff's syndrome characterized by chronic amnesia (Kopelman, 2002).

Slingedael offers a long-stay facility for patients with Korsakoff's syndrome in Rotterdam, The Netherlands. For triage purposes, confused alcoholic patients with probable Wernicke-Korsakoff's syndrome related cognitive disorders are visited by our physicians and psychologists, usually when they are inpatients of general or psychiatric hospitals in the Rotterdam region (~1.2 million inhabitants). In daily practice, we see very disappointing results with respect to the quantity of patients that have been appropriately treated with parenteral thiamine after admission to general or psychiatric hospitals. In fact, up to 90% of the confused alcoholics that have been visited by members of our team did not receive parenteral thiamine or received parenteral thiamine just once. This while current Dutch recommendations state that confused inpatients *at risk* of developing WE should receive 250 mg i.m. or i.v. for at least 3 to 5 days; up to 500 mg i.v. for patients that have presumed WE (Van den Brink and Jansen, 2009). Implementations of the guidelines have been documented (Laurent and van der Schrieck - de Loos, 2009).

Therefore, we suggest that besides the clarity of the guidelines for treatment of WE also successful propagation for treatment guidelines is necessary to prevent the detrimental effects of unsuccessfully treated WE, namely Korsakoff's syndrome.

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The Tangible Common Denominator of Substance Use Disorders: A Reply to Commentaries to Rehm *et al.* (2013a)

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Abstract — In response to our suggestion to define substance use disorders via ‘heavy use over time’, theoretical and conceptual issues, measurement problems and implications for stigma and clinical practice were raised. With respect to theoretical and conceptual issues, no other criterion has been shown, which would improve the definition. Moreover, heavy use over time is shown to be highly correlated with number of criteria in current DSM-5. Measurement of heavy use over time is simple and while there will be some underestimation or misrepresentation of actual levels in clinical practice, this is not different from the *status quo* and measurement of current criteria. As regards to stigma, research has shown that a truly dimensional concept can help reduce stigma. In conclusion, ‘heavy use over time’ as a tangible common denominator should be seriously considered as definition for substance use disorder.

We thank their authors for the four commentaries (Bradley and Rubinsky, 2013; Heather, 2013; Rice, 2013; Saunders, 2013) on our suggestion to replace the current definitions of substance dependence, use disorders, abuse and harmful use by heavy use over time (Rehm *et al.*, 2013a). Here, we attempt to answer the points raised.

We see four major threads of discussion:

- (a) Theoretical considerations that the essence of addictions is different than currently defined by DSM and ICD, and that the reformulation of heavy use over time does not capture this point (Heather, 2013; Saunders, 2013). This has a corollary that definitions other than heavy use over time or heavy use over time itself can better explain phenomena currently associated with addictive behaviour (Bradley and Rubinsky, 2013; Saunders, 2013).
- (b) Problems with assessing heavy consumption over time (Bradley and Rubinsky, 2013; Saunders, 2013).
- (c) The usefulness of various concepts in reducing stigma and in clinical practice (Bradley and Rubinsky, 2013; Rice, 2013).
- (d) Using heavy use as one of several criteria for defining substance use disorders (Bradley and Rubinsky, 2013).

Starting with the theoretical considerations, we made our arguments that almost all of what is currently conceptualized under the heading of addiction or use disorders is a consequence of heavy use over time (Rehm *et al.*, 2013a). Obviously, we used the current definitions of DSM IV, DSM 5 and ICD 10 as starting points. Both Rice and Saunders note that these definitions have strayed quite far from the single dimension of Saunders’ ‘internal drive’—the dimension that has been at the heart of the addiction concept as it was invented in post-Enlightenment European cultures (Levine, 1978). As Rice notes, DSM-5’s adoption of the term ‘substance use disorder’ further cements this separation.

The addiction concept essentially puts forward an explanation rather than a description: an explanation in terms of a mysterious force driving behaviour. In the wake of the St. Louis revolution in psychiatric nosology (Room, 1998), psychiatric classification in the USA, and increasingly elsewhere, has favoured description over the kind of psychodynamic hypothesis represented by the classic addiction concept. An explanation in terms of a mysterious force that cannot be fully modelled in animal or neurobiological research can actually be argued to be obstructive of scientific progress.

However, we agree that the situation ‘that some people continue to use heavily despite knowing that their heavy use

is causing the negative consequences’ (Heather, 2013) is worth continued investigation (see also (European Monitoring Centre for Drugs and Drug Addiction, 2013), where this concept is discussed in more detail), and in fact one of the authors has emphasized the importance of investigating automatically triggered or implicit processes in substance use disorders (Wiers and Stacy, 2006), exactly to understand these psychological processes. However, while these processes may be associated with the phenomenon of continued heavy use they are not necessary to characterize it.

When we scrutinize the additional criteria proposed by the commentators, we do not see a necessity to include other criteria. For instance, all the correlations with other phenomena that Saunders (2013) cites to demonstrate what he believes is the core of addiction and its consequences are also true for heavy use over time. To give an example, the amount of heavy use over time is highly correlated with the number of criteria fulfilled in current definitions; so, it is no surprise that the correlations with outcomes are similar. To illustrate this, we have undertaken a cross-tabulation of alcohol dependence (last year) with level of use in the US National Epidemiologic Survey on Alcohol and Related Conditions, separated by treatment status (see Table 1). The more symptoms, the higher the consumption, with higher consumption in people with lifetime treatment. Similarly, in a Catalonian cohort of people treated for alcohol dependence, level of use, sex and age ‘explained’ 94% of the variance of DSM III R symptoms (for a description of the cohort (Gual *et al.*, 1999)). Significant associations were also found in the 2012 German Epidemiological Surveys of Substance Abuse, not only for alcohol but also for tobacco, cannabis and cocaine (data not shown; for a description see (Kraus *et al.*, 2013)). To conclude: all relevant effects used to demonstrate the evidence for the usefulness of current criteria or for the number of criteria as a measure of severity would be replicated by levels of heavy use, as the two measures are highly correlated. And as demonstrated in our original paper, the heavy use over time concept better explained the relationships with negative health outcomes (Rehm *et al.*, 2013a).

Thus, as heavy use over time is the simplest concept, we should just use this, unless there are clear indications that other concepts better explain relevant phenomena that heavy use over time cannot do. As for the understanding of an ‘internal drive’ (Saunders, 2013), we believe that it is enough that heavy use over time leads to changes in the brain, which

Table 1. Average alcohol intake in grams per day by number of DSM-IV criteria fulfilled for alcohol dependence (last year), by whether treated in lifetime: from data of the US National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

Gender	Number of criteria of DSM-IV for alcohol dependence							
	0	1	2	3	4	5	6	7
For people who have never been in treatment								
Men	9.1	27.1	35.9	56.5	73.6	88.0	107.4	189.0
Women	4.1	13.6	19.8	23.6	48.5	56.7	108.8	114.5
Total	6.6	21.6	29.5	45.4	64.7	77.5	107.8	170.3
For people who have been in treatment in their lifetime								
Men	20.6	35.2	98.2	75.2	109.1	124.2	119.8	214.1
Women	10.1	20.3	23.5	19.8	37.9	55.5	275.1	230.4
Total	17.5	31.7	77.9	61.5	91.2	104.7	165.1	218.3

are linked to the behavioural expressions seen in ‘addicted’ people. We did not touch on whether such behaviour is voluntary or not, or under what circumstances it can be reversed. Clearly, there are good examples for reversal of behaviour (e.g. of heavy heroin use over time in Vietnam veterans (Robins, 1993)), whereas some changes in the brain such as the reduction of the number of dopamine receptors in people with heavy used over time may be more permanent (Daglish *et al.*, 2001; Volkow *et al.*, 2011). However, it is important that consequences such as mortality are mainly linked to the behaviour, i.e. to the level of heavy consumption over time (Rehm *et al.*, 2013a; Rehm and Roerecke, 2013; Roerecke *et al.*, 2013).

What about the examples given for socio-economic differentials of consequences? The higher mortality risk associated with heavy use can be found in all economic strata (for a striking example: (Rossow and Amundsen, 1996)), but in most studies, people in higher economic strata experience less mortality and other consequences per alcohol consumed than poorer people (Schmidt *et al.*, 2010). This has to do with better access to care, less interactions with other risk factors (e.g. smoking, nutrition) and a better constellation of environmental factors. Thus, across the whole range of diseases and disorders, people with higher socio-economic status tend to have lower mortality rates for the same behaviours or the same disease categories (Huisman *et al.*, 2005; Lantz *et al.*, 2010). We do not see, however, why the current definition of substance use disorders should have any advantage in this respect.

As for measuring heavy use over time, the psychometric qualities of measuring level of use for alcohol and tobacco or frequency of use for other substances are no worse than those that measure current criteria for substance use disorders. Of course, in clinical interviews, some people may underreport actual consumption, but the same is true for current criteria. In addition, clinical practice rarely goes through diagnostic criteria one by one anyway. In clinical interviews, we imagine a process similar to high blood pressure (see Nutt and Rehm, 2013). After having established high blood pressure, doctors may ask about other signs, potentially relevant behaviour (e.g., salt intake, behavioural factors leading to higher BMI) or family disposition for cardiovascular outcomes linked to high blood pressure such as stroke. For heavy use over time, similar questions may be asked. But this does not mean that such answers to such questions would be used for establishing diagnoses of hypertension or heavy use over time.

Finally, as for the cultural bias for loss of control, we presented evidence comparing Latvian and Italian survey results, with multifold differences in alcohol dependence prevalence, which in our view cannot be explained otherwise (Rehm *et al.*, 2013a). The differences between alcohol dependence prevalence in Latvia and Italy are typical for a North-South difference in Europe (Rehm *et al.*, 2012; see also Rehm *et al.*, 2005): per litre of pure alcohol consumed per capita, the prevalence of alcohol dependence in Baltic and Nordic countries is 4–5 times the rate in Southern countries (the latter defined as comprising Cyprus, Greece, Italy, Malta, Spain, Portugal). Associated indicators such as heavy drinking prevalence or liver cirrhosis mortality do not show multifold differences of this magnitude between regions (Rehm *et al.*, 2012; details for Latvia and Italia, see Rehm

et al., 2013a). While more research is necessary, we tried to explain these differences by a cultural bias that would prescribe that in Southern Europe one would not traditionally admit to losing control over one’s drinking, whereas losing control may be the very reason for many drinking occasions in the Nordic and Baltic countries (Room, 2006, 2007). Survey results tend to further support this reasoning: Italians have much more drinking with meals (for level see http://www.rssp.salute.gov.it/rssp2011/documenti/RSSP_2011_Inglese_web.pdf; for comparative figures with Nordic and other countries, see Leifman, 2002), i.e. in more controlled and ritualistic settings (Marshall, 2005). Also, Italians drink comparatively less per occasion (Leifman, 2002), and while they associate less negative consequences with their drinking (Landberg, 2012), they indicated a high level of informal control (Reitan, 2004). When looking for a definition of substance use disorders, these differences favour drinking over time in our view, as this definition is better aligned with mortality and health burden (Rehm *et al.*, 2013b) than the current measure, where you get multifold differences associated with cultural variables more than with health burden.

Stigma is a major problem in all treatment of mental disorders, but is particularly so with substance use disorders (Üstün *et al.*, 2001). There are no simple ways to deal with stigma and exclusion in health care, but empirical research has shown that stressing dimensional aspects of disease may help reduce stigma (Schomerus *et al.*, 2013). Thus, beliefs that mental disorders are defined by putting thresholds on an underlying continuum were associated with more positive emotional reactions and less desire for social distance. Unfortunately, for substance use disorders, such continuum beliefs are not that pronounced. For instance, in a German representative survey, only 27% of respondents believed in a continuum for alcohol use disorders, a similar percentage as for schizophrenia (26%), but less than for depression (42%; (Schomerus *et al.*, 2013)). Thus, it is no surprise that alcohol use disorders are particularly stigmatized (Schomerus *et al.*, 2011), not only in Germany, and even in comparison with depression and other mental disorders. This is consistent with people with alcohol use disorders having the largest treatment gap of any mental disorder (Alonso *et al.*, 2004; Kohn *et al.*, 2004; Rehm *et al.*, 2013b). Thus, a clearly dimensional concept such as heavy drinking over time may help. Compared with other essentially dimensional concepts, for example the number of DSM-5 (American Psychiatric Association, 2013) criteria as an indicator of level of severity, heavy use over time is simpler to understand, and is not *per se* associated with psychiatric problems, thus being more suitable to reduce stigma than dimensional approaches based on psychiatric diagnoses, like the DSM-5.

Nutt and Rehm (Nutt and Rehm, 2013) have recently laid down an alternative approach to alcohol use disorders based on heavy drinking, which would be analogous to blood pressure. It stresses the continuous rather than dichotomous nature of the heavy drinking measure. This is not to say, that cutting down drinking or achieving abstinence is easy or a matter of will only (in fact, the approach explicitly calls for improving pharmacologically assisted interventions), but such an approach will likely reduce stigma, as well as have preventive aspects, points put forward nearly 30 years ago by the UK Royal College of General Practitioners in its report ‘Alcohol—a Balanced View’ (Anderson *et al.*, 1986).

Finally, Bradley and Rubinsky (2013) as others before (Li *et al.*, 2007) suggest to use heavy use over time as one of several criteria for defining substance use disorders. Again, such a more complex definition would be necessary, if the combined definition could explain more relevant phenomena or otherwise show better predictive power. This is an empirical question. We have yet to be convinced of one important phenomenon that cannot be explained by a 'heavy use over time' definition, but that can be explained by a more comprehensive definition.

In conclusion, we believe that heavy use over time should seriously be considered as the best definition for what is currently called substance use disorders or dependence. Of course, since it is a continuum, thresholds will have to be set similar to setting thresholds for raised blood pressure (which have changed historically and are conditioned by treatment options and concurrent diseases) or for many other diseases in ICD (Rose, 1992). These seem to be common procedures and do not preclude reimbursement of treatment or fall outside current medical practice. When levels of use increase, more negative consequences occur. However, the primary criterion should be heavy use, because it also points in the direction of what can be done to counter the negative consequences (which does not mean that this is always easy, and should not be aided).

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