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Review

REGIONAL DIFFERENCES IN ANXIOLYTIC PRESCRIBING IN LIGHT OF HOFSTEDE'S CULTURAL DIMENSIONS THEORY

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SUMMARY

Background: *Anxiolytics such as benzodiazepines are widely used in the treatment of anxiety disorders, although they are no longer recommended as first-line therapy for these conditions due to increased risk of dependence, as well as cognitive adverse effects, especially among the elderly. High prescribing rates of anxiolytics may be indicative of higher prevalence of anxiety-related phenomena in a given society, either in a form of an anxiety disorder or as pressure on physicians to keep prescribing them, against current guidelines.*

Subjects and methods: *We inspected prescribing rates of anxiolytics in 21 European countries and compared them with six dimensions of Hofstede's cross-cultural framework, namely uncertainty avoidance (UAI), power distance (PD), individualism (IDV), masculinity (MAS), long-term orientation (LTO) and indulgence (IND).*

Results: *According to our findings, anxiolytic prescribing patterns in selected European countries correlate positively with Hofstede's dimensions of UAI and PD and negatively with IDV.*

Conclusion: *Differences in prescribing rates of anxiolytics and trends in their use may be affected by cross-cultural factors. More research is needed to shed light on these regional differences in anxiolytic prescribing.*

Key words: *anxiety - anxiolytics - benzodiazepines - cross-cultural - Hofstede - prescribing*

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INTRODUCTION

Anxiety is an emotion characterized by uneasiness and overwhelming feelings of worry, normally occurring as a reaction to a situational setting identified as threatening by the experiencer. Normal, intermittent anxiety is a motivating force, vital to one's behavior. On the other hand, pathological anxiety stands in the way of independent everyday functioning. Anxiety is, more often than not, considered a future-oriented emotion, because it involves the anticipation of menaces to come. This anticipation or expectation may produce anxiety because the future is inherently undetermined and unknown (Grupe & Nitschke 2013). Anxiety is phenomenologically and neurobiologically related to fear, which is a present-oriented mood state, a reaction to ongoing danger. Anxiety disorders are relatively common, with lifetime prevalence of around 30% (Kessler et al. 2012). Societies differ in cultural, social, and contextual factors which may influence prevalence of anxiety disorders as well as affect possible therapeutic choices, and consequently, treatment outcomes. Cultural influences have mostly been studied in some specific anxiety disorders, like social anxiety disorder (Hofmann & Asnaani 2010), but they still need to be thoroughly researched in other anxiety disorders.

Anxiety and fear are considered learned states, prone to "threat conditioning" (Le Doux 2014). Maladaptive learning, involving brain regions such as amygdala and hippocampus, leads to emotional dysregulation (Likhtik & Paz 2015). Intensified threat anticipation, which is due to amygdala-related vigilance increase and erroneous associative learning, creates a feedback loop which renders anxious subjects even more vigilant and watchful of subjective threat (Grupe & Nitschke 2013). Maladaptive learning can be corrected by means of cognitive-behavioral therapy, which is a treatment of choice for anxiety disorders and related disorders in adults (Carpenter et al. 2018), either alone or in combination with one antidepressant of selective serotonin reuptake inhibitor (SSRI) class, which are proven to be neuroprotective (Young 2002). Second-line treatment includes antidepressants of other classes, while anxiolytics, of which benzodiazepine are the most used class, are nowadays relegated to third-line therapy (Baldwin & Huneke 2020).

There are many reasons why benzodiazepines are no longer considered first-line treatment for anxiety disorders, with tolerance and physical and psychological dependence being just one of them (Roy-Byrne et al. 1993, Vinkers et al. 2012). Due to euphoric effects, they have addictive potential in susceptible subjects (Ciraulo et al. 1988). More importantly, they have deleterious effects on cognition. They reduce the speed of attentional performance (Snyder et al. 2005), slow learning processes (Rostock et al. 1989) and compromise associate learning (Pietrzak et al. 2012). They impair context integration processes (Münte et al. 1996), as well as block memory consolidation (Olofsson et al. 2011). Their use correlates with increased levels of forgetting (Allen et al. 1991), lower cognitive flexibility (Contreras-González et al. 2015) and prospective

memory impairment (Rich et al. 2006). Furthermore, they were found to disrupt recognition of facial emotions (Coupland et al. 2003). They can cause anterograde amnesia, independent of the degree of sedation (Verwey et al. 2004). Taking all these findings into consideration, it comes as no surprise that they interfere with effectiveness of cognitive-behavioral therapy (Otto et al. 2010, Eppel & Ahmad 2016), the therapy of choice in treatment of anxiety disorders. Last, but not least, association between the chronic use of benzodiazepines and the development of dementia, has been suggested (Lucchetta et al. 2018).

Subjects' inclination to prefer benzodiazepines may be due to their rapid onset of action, but possible euphoric effects should not be ignored, especially in vulnerable people, such as those suffering from substance use disorders or personality disorders (Ciraulo 1988). Due to similarity of their psychological and neurocognitive effects, they have been compared to "alcohol in a pill" (Lembke 2016, Lembke et al. 2018). Their cognitive adverse effects, just in the case of alcohol use, may not be obvious to their users; still, they can be noticeable to others in their surroundings. To complicate things even further, taking a potent, rapid-onset tranquilizer has been described as a form of avoidance behavior (Melaragno et al. 2020).

Higher prescribing rates of anxiolytics may be suggestive of higher prevalence of anxiety-related phenomena in a given society. We investigated how anxiolytic prescribing rates in European countries correspond with cultural dimensions of Hofstede's theory.

Hofstede's cultural dimensions theory (Hofstede 2007) is a foundation for research in in cross-cultural psychology and cross-cultural communication. It was elaborated by Geert Hofstede who borrowed some concepts from Cyert's "behavioral theory of the firm" (Hofstede 2020) and applied them to the level of organization, consequently expanding on it in order to describe differences between national societies (De Mooij & Hofstede 2010). Practical applications of the theory can be seen not only in international communication, management or marketing, but can also be expanded to all spheres of cross-cultural communication, including psychology, medicine and public health (Verma et al. 2016). Hofstede's cultural dimensions theory features six dimensions, known as: uncertainty avoidance (UAI), power distance (PD), individualism (IDV), masculinity (MAS), long-term orientation (LTO) and indulgence (IND).

The uncertainty avoidance index (UAI) is defined as "extent to which the members of a culture feel threatened by ambiguous or unknown situations" (Hofstede 2020). High-UAI societies are likely to have strict codes of behavior, need for numerous laws or regulations, which eventually may not even be enforced. Uncertainty is usually seen as something negative, to be dealt with. The desire to control the future creates an atmosphere with high levels of stress and anxiety, which leads to strong emotional reactions and occasionally aggression. In such societies, changes are frequently opposed, there is slow adoption of innovations; there is low acceptance of being different, which gives rise to prejudices such as xenophobia. Uncertainty-accepting societies (low-UAI societies) are known for flexibility, tolerance, and innovation; there are fewer regulations; uncertainty is seen as a part of life. People in these societies tend to look forward to the future, and embrace it with optimism, which results in lower levels of stress and anxiety. In these societies, strong emotions as well as aggression are normally subdued. UAI is not to be mistaken for risk avoidance; members of an uncertainty-avoiding society still take risks, as long as they think they know them (Hofstede 2020). High UAI is in close connection with low well-being (Hofstede 2007) and is related to the personality trait neuroticism (Hofstede & McCrae 2004, Taras et al. 2010). It was found that subjects high in UAI were more likely to make extremely negative interpretations of only mildly negative scenarios and consequently were prone to escalating avoidance behaviors (Stopa & Clark 2000). Researchers also discovered a negative link between high UAI and prosocial behavior (Handy & Cnaan 2007). Older age is associated with lower well-being in countries higher in UAI but not in countries lower in UAI (Lawrie et al. 2020). A survey study of 13,616 air traffic management employees in 21 European countries found a negative association between safety culture and UAI. In high-UAI counties, staff attitudes towards safety-related practices (such as anxiety over the embarrassment of making an error) influenced responses on the safety culture survey, such as on incident reporting (Noort et al. 2016). On a more individual level, an fMRI study detected neurobiological differences between uncertainty acceptance and uncertainty avoidance. During information gathering, uncertainty avoidance was found to correlate with activations of the right middle frontal cortex, whereas effects of uncertainty acceptance were found within the superior frontal cortex, the insula and precuneus (Krug et al. 2014).

The power distance index (PD) is defined as "the extent to which the less powerful members of organizations and institutions (like the family) accept and expect that power is distributed unequally" (Hofstede 2020). In high-PD societies, children, from the early years, learn respect as a key ideal. Society is overly hierarchy-bound, yet centralized. Inequality is accepted as something normal. Superiors are in charge while subordinates expect to be told what to do. On the other hand, in low-PD societies, children, from the early age, are encouraged to be independent. Hierarchy is loose, it serves for practical purposes, power is oftentimes distributed; inequality is seen as unsound. In such societies,

there is more decentralization and more efficient teamwork; those in subordinate positions expect to be consulted (Hofstede 2020). In a recent analysis, it was found that people from societies with stronger anti-hierarchical and more egalitarian cultures (scoring low on PD) tend to evaluate their national health system more positively (Borisova et al. 2017).

Individualism vs. collectivism (IDV): this index explores the "degree to which people in a society are integrated into groups". High-IDV (highly individualistic) society is a society with loose connections between individuals: everyone is expected to look after oneself and immediate family only. Low-IDV (highly collectivistic) society is a society in which individuals are taught, from their birth, to be part of coherent in-groups (Hofstede 2020). High-IDV societies feature "I"-identity, low-context communication, and tasks before relations. While other sub-parts of society are classified as individuals (which is a concept of universalism), there is much competition between individuals, which as a result make it a more dynamic society. Low-IDV societies have "we"-identity, high-context communication and relations before task. In such cultures, individuals are classified only as members of in- our out-groups (concept of exclusionism). In-group harmony is to be preserved, to secure the competition between "tribes" (Hofstede 2020). IDV may influence cognitive functions, such as individual memory perspective during memory retrieval. It was found that people from high-INV cultures are more likely to possess a field (first person) perspective, while people from low-INV societies are more likely to take an observer (third person) perspective (Martin & Jones 2012). INV can affect public health actions. It was discovered that individualistic societies showed faster adoption of smoking but also faster cessation of tobacco use (Lang et al. 2015).

Masculinity vs. femininity (MAS): a high masculinity society is defined as "a society in which emotional gender roles are distinct: men should be assertive, tough and focused on material success, women on the quality of life". In a low-MAS society, femininity predominates. It is "a society in which emotional gender role overlap: both men and women are supposed to be modest, tender, and focused on the quality of life" (Hofstede 2020). In masculine societies, work is seen more important than family, the strong are venerated, while the weak are ridiculed. One almighty God is the center of attention in religious practices. On the other hand, in feminine societies, humility, modesty, and egalitarianism are encouraged, while isolated high achievers are not admired. People balance family and work. Weak are to be protected. Religion is less ceremonial, with the preferable focus on people (Hofstede 2020). Analyses of data collected in 14 nations in Europe showed that high MAS was an independent predictor of higher national depression levels (Arrindell et al. 2003). High MAS is deemed incompatible with the concept of the happy nation (Steele et al. 2018).

Long-term orientation vs. short-term orientation (LTO): associates the connection of the past with the current and future challenges. Long-term oriented societies are characterized by common sense, humbleness, relativity of the concept of good and bad, high adjustability of norms according to the situation, willingness to learn from foreign experiences and challenge local traditions. Short-term oriented (low-LTO) societies are rigid in their normative, ideological, as well as religious organization, overly self-oriented and self-sufficient; therefore, we can presume that tradition may impede progress (Hofstede 2020). High LTO-societies tend to be economy-conscious; in a recent survey there was found a negative correlation between LTO and donating money or helping a stranger (Guo et al. 2018).

Indulgence vs. restraint (IND): this dimension refers to the degree of freedom that societal norms give to citizens in fulfilling their human desires. High-indulgence society is defined as "a society that allows relatively free gratification of basic and natural human desires related to enjoying life and having fun". Its counterpart, a highly restrained society, is defined as "a society that controls gratification of needs and regulates it by means of strict social norms". In high-IND societies, people tend to be more extroverted, optimistic and to feel happier as well as healthier; they feel the life is under their control. Having friends is considered particularly important, as is active participation in sports. There is less moral discipline. In low-IND, that is, highly restrained societies, people tend to be more introverted, pessimistic, or cynic, less happy and less healthy. There is more work ethic, stricter moral discipline, including stricter sexual mores. They tend to justify their actions as being due to some external event (Hofstede 2020). Variability in market uptake of psychotropic medications in Europe was found to reflect cultural diversity, with IND being the cultural dimension correlating positively, albeit marginally, with the utilization of new psychotropic medications (Hoebert et al. 2017). Researchers have also found a positive link between IND and prosocial behavior (Guo et al. 2018), but also a positive correlation between higher IND and a higher BMI. A higher mean BMI was also found to be significantly associated with higher dimensions of INV, UAI and MAS, but with lower PD (though only in males) and lower LTO (males only) (Wallace et al. 2018).

Culture seems crucial for both individual and national well-being; the happy nation, with optimal subjective well-being, is likely to have low PD, low UAI, low MAS but high INV (Steel et al. 2018). In a survey of phobic anxiety in eleven countries, it was revealed that high UAI and high MAS predicted higher

national levels of fear (except for social fears), with MAS additionally predicting some specific forms of fear, such as agoraphobic fears (Arrindell et al. 2004). Road-traffic accident fatality rates were found to correlate positively with PD, UAI and LTO and negatively with IDV and MAS (Gaygisiz 2009). Cultural values were also examined as predictors of suicide incidence. PD, UAI and MAS were found negative correlates of reported suicide, while INV was a strong positive correlate, except in the case of young women, where negative correlation was found (Rudmin et al. 2003). In subsequent, more extensive studies, suicide incidence again correlated positively (and significantly) with IND, but negatively with PD, in the general sample (Lenzi et al. 2012). Nonetheless, it was observed that nations with traditional values had low suicide rates, whereas countries with very high secular or rational values could have either high or low suicide rates. In the subset of secular, posttraditional countries taken from the same sample, obtained results were strikingly different: suicide rates correlated positively with PD and UAI, but negatively, albeit marginally, with IDV, even though all correlations were not significant (Lenzi et al. 2012).

Cultural factors can influence prescribing of medications, including antibiotics and psychotropics. Lower education level and governance quality, higher PD, MAS and UAI, as well as national personality characteristic neuroticism seem related to higher antibiotic use rates in European countries (Gaygisiz et al. 2017). Overprescribing of antibiotics can lead to bacterial resistance. The epidemiology of methicillin-resistant Staphylococcus aureus (MRSA) infection shows an evident geographical pattern in Europe, reflecting differences in cultural dimensions: MRSA proportions were found to correlate positively with dimensions of UAI and MAS, but negatively with LTO (Borg et al. 2012). Prolonged perioperative surgical prophylaxis within European hospitals correlates positively with UAI as well (Borg 2014). In a study of antidepressant use in five European locations (Sweden, Denmark, Norway, Catalonia and Veneto), antidepressant use was found to correlate negatively, but not significantly, with socio-cultural dimensions of INV, MAS and LTO (Gomez-Lumbreras 2019).

SUBJECTS AND METHODS

We inspected prescribing rates of anxiolytics (N05B) in 21 European countries during the year 2017 and compared them with six dimensions of Hofstede's cross-cultural framework (Hofstede 2020). The scrutinized countries were: Austria, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hungary, Iceland, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom and Croatia.

The defined daily dose (DDD) methodology was chosen, adjusted for population size and time framework. By World Health Organization definition, DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (WHO 2020). The measure DDD per 1000 inhabitants per day (DDD/TID), a frequently used measure in drug use comparison, can suggest what portion of a population is extensively using a drug or class of drugs. For Croatia, the data were retrieved from the official site of Croatian Agency for Medicinal Products and Medical Devices (HALMED 2020). The data for the remaining twenty European countries surveyed here were extracted from the official statistical data obtainable from the internet pages of the Organization for Economic Co-operation and Development (OECD). Country-dependent values of Hofstede's six cultural dimensions were obtained from the author's official internet site (Hofstede 2020).

Observed differences in prescribing of anxiolytics between countries were substantial. The starkest difference was noted between high-anxiolytic-prescribing countries like Portugal (93.9 DDD/TID) and low-anxiolytic-prescribing countries such as Germany (3.4 DDD/TID). With DDD/TID of 75.84 in 2017, Croatia can be considered the example of a high-anxiolytic-prescribing country, with marked increasing trends of prescribing of antianxiety drugs (78.64 DDD/TID in 2018 and 79.09 DDD/TID in 2019; HALMED). High consumption of antianxiety drugs in Croatia was identified as a public health problem more than fifteen years ago (Culig et al. 2005), but this has virtually been ignored and no measures have been taken to reduce their inappropriate prescribing. In Croatia, anxiolytic drug use in the last twenty years can almost completely be attributed to benzodiazepines. Presently, the most popular drugs of this class are diazepam and alprazolam (HALMED 2020). Drug manufacturers are not directly to blame for this situation because they provide prescribing information in medication package inserts of these drugs, explaining that benzodiazepines are not recommended for long-term use, explicitly stating the maximal time interval of their use (from 4 up to 12 weeks, depending on the specific drug). Nevertheless, this recommendation is often disregarded by patients, as well as prescribing doctors, resulting in high, long-term, consumption of benzodiazepines, compared to other countries in Europe, as well as underprescribing of SSRI antidepressants (Potočnjak et al. 2018) which are considered first-line treatment for anxiety disorders, according to current evidence-based European guidelines (Baldwin & Huneke 2020).

Anxiolytic prescribing data was submitted to statistical analysis. DDD/TID values were tested for linear relationships with Hofstede's cultural dimensions of UAI, PD, INV, MAS, LTO and IND. Pearson product-moment correlation coefficient was calculated. Statistical significance was set at $p<0.05$.

RESULTS

This population-based study showed that anxiolytic use varies significantly across selected European countries. The patterns of similarity or differences between them are in correlation with three Hofstede's cultural dimensions: uncertainty avoidance, power distance and individualism (Table 1).

Table 1. Correlations between prescribing rates of anxiolytics in 2017 in 21 European countries (in DDD/TID) and Hofstede's cultural dimensions

Dimension	Correlation (r)	r^2	Significance (p)
UAI	0.5840	0.341	0.0054
PD	0.4290	0.184	0.052
IDV	-0.6250	0.390	0.002
MAS	-0.0210	0.0004	0.929
LTO	-0.2569	0.066	0.260
IND	-0.3359	0.130	0.137

There was found a strong, positive (r=0.584), statistically significant (p=0.005) correlation between uncertainty avoidance and rates of prescribing of anxiolytic drugs. We also detected a moderate (r=0.429), borderline-significant (p=0.052), correlation between power distance dimension and antianxiety drug use. In addition, we found a strong, negative (r=-0.625), statistically significant (p=0.002), correlation between the dimension of individualism and consumption of anxiolytics. The dimension masculinity was not found to correlate with benzodiazepine prescribing. Other two dimensions (long-term orientation and indulgence) were found to be in moderate, but statistically not significant, negative correlation with anxiolytic use in selected countries.

While anxiolytic use per se may not be utterly indicative of prevalence of anxious disorders in a specific country, it may, indirectly, be indicative of inappropriate management of anxiety, or a disconnect between efficient diagnosing and finding or providing efficacious treatment. In other words, high prescribing rates of anxiolytics may be indicative of higher prevalence of anxiety-related phenomena in a given society, either in a form of an anxiety disorder or as pressure on physicians to keep prescribing them, against current guidelines.

We are going to discuss the results in light of previous studies that investigated anxiety and anxiety-proneness in cross-cultural contexts. It comes as no surprise the fact that uncertainty avoidance is positively correlated with overprescribing of certain classes of drugs, such as anxiolytics, as revealed in our current study, or antibiotics, as seen in aforementioned surveys. In societies with high uncertainty avoidance, ambiguity and uncertainty are not easily tolerated, which makes people, both doctors and patients, want to act promptly in health-related settings. Thus, there might be strong preference for rapid-onset medications, including benzodiazepines. Upon consumption, subjects feel immediate relief and may end up liking the drug which can result in entering a vicious cycle of chronic benzodiazepine use, with harmful cognitive consequences in the long run. Likewise, higher power distance dimension can create certain fears of communicating with others, which can contribute to situational anxiety. Rather unexpectedly, individualism was found a protective factor for the use of antianxiety drugs, being in strong negative correlation with benzodiazepine use in our study. One can presume that, in individualistic countries, there is much less pressure on individuals to fit in, which alleviates potential stress and subsequent anxiety, therefore eliminating need for antianxiety medication. This is in line with aforementioned studies linking low individualism with failure to create the happy society (Steel et al. 2018).

CONCLUSION

In many high UA, high PD, low INV countries, such as Croatia, prescribing of anxiolytics is spiraling out of control, due to inappropriately high dosing or prolonged use (Marić et al. 2017, Delaš Aždajić et al. 2019), paradoxically, giving rise to an anxious society. Anxiety disorders should be treated following the guidelines created on the principles of evidence-based medicine, and not on personal, individual fallacies. First-line treatments, such as SSRI antidepressants and/or cognitive-behavioral psychotherapy should be recommended and easily provided to people (Bui et al. 2019). Thus far, in Croatia, there are no national guidelines on treatment of anxiety disorders or on appropriate use of benzodiazepines.

As we could see, differences in prescribing rates of anxiolytics and trends in their consumption may be affected by cross-cultural factors. More research is needed to shed light on these regional differences in anxiolytic prescribing and how they affect treatment outcomes.

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Conflict of interest:

All authors report no biomedical financial interest or potential conflicts of interest.

The publication of this study has been approved by the Ethics Committee of the institution within which the work was undertaken and it conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000).

Contribution of individual authors:

All authors contributed to writing of this paper equally.

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