An international study of analgesic dependence among people with pain in the general population

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Abstract

Background: Overuse of and dependence on analgesics (including opioids and other pain medications) are major international public health problems.
Objective: To identify influences on analgesic dependence among analgesic users in the general populations of different countries.
Methods: Online surveys of 1,283 people with pain in the UK, USA, Australia, Germany, Egypt and China/Macau/Hong Kong.
Results: Levels of analgesic overuse and dependence were highest in Egypt and lowest in China/Macau/Hong Kong. In every country except Egypt, frequency of pain and frequency of analgesic use were correlated with analgesic dependence, and scores on the Need subscale of the Pain Medication Attitudes Questionnaire (PMAQ; McCracken et al., 2006) independently predicted analgesic dependence. In the UK, USA, Australia and Germany, frequency of analgesic use mediated the effects of pain frequency or intensity, and Need scores mediated the effects of frequency of analgesic use. In Egypt, more recent pain, analgesic overuse, and the Emotion and Solicitude subscales of the Survey of Pain Attitudes (SOPA) independently predicted analgesic dependence.
Conclusions: Across multiple countries, the impact of pain on analgesic dependence was mediated by frequency of analgesic use rather than overuse or abuse, and self-reported need for analgesics was the strongest independent predictor of dependence. Asking people directly about their feelings of needing analgesics could therefore identify those who could be helped to use analgesics less frequently, which should reduce their risk of dependence.
Keywords: Analgesic dependence; general population; international

Glossary of key terms

Term	Definition
Analgesics	Pain medications, or painkillers (including opioids and other pain medications)
Analgesic overuse	Using analgesics at higher doses than recommended or for longer than recommended
Analgesic misuse	Another term for analgesic overuse
Analgesic abuse	Using analgesics when not in pain

Introduction

Analgesic overuse (or 'misuse') is a major international problem. A review of 65 studies in Europe showed that opioids were the most commonly misused analgesics, but rates of misuse varied considerably between countries (Casati et al., 2012). Prescribed opioid analgesics are probably the biggest part of the problem, but non-prescribed (or 'over-the-counter') opioid and non-opioid analgesics are also associated with overuse, abuse and dependence (Fingleton et al., 2016).

A large general population survey in 15 European countries found that two-thirds of people with chronic pain used prescription analgesics and half used non-prescription analgesics. In addition, 40% reported inadequate pain management, 63% worried about side effects and 38% were afraid of addiction to pain medication. Use of strong opioids varied from 0-1% in Italy and Spain to 12-13% in the UK and Ireland. Use of weak opioids varied from 5-13% in Italy, Spain, Denmark and Israel, to 50% in the UK and Norway (Breivik et al., 2006). A comparable survey in the USA found that 4.8% of respondents had misused or abused prescription analgesics, and analgesic misuse or abuse increased the risk of general substance use or dependence disorder three years later (Boyd et al., 2009).

Analgesic use is affected by access and availability, which differs between the USA, where analgesics are more available, and Europe, where there are more controls on the purchase of over-the-counter medications (Cohen et al., 2004). For example, compared with students in Germany, students in the USA took more analgesics, used more different types of analgesic, bought more analgesics at non-pharmacy outlets, and were less likely to consult a doctor when in pain (Hanoch et al., 2007).

Surveys in developing countries such as Egypt, Lebanon and Pakistan often show very high rates of analgesic use, which is often attributed to availability without prescription (Benjamin et al., 1996; Ghandour et al., 2012; Mumtaz et al., 2011; Sallam et al., 2009; Zafar et al., 2008). A survey in Lebanon, for example, found that analgesics were the most commonly used type of prescribed medication, and 63% of respondents reported that prescription pain medications would be easy or very easy to obtain without a prescription (Ghandour et al., 2012).

A pharmacy dispensing analysis in Egypt showed that similar medicines were dispensed with and without a prescription (Benjamin et al., 1996). Interviews with pharmacy customers in Egypt showed that 81% purchased self-medication but most had poor knowledge of the drugs involved, and some medications available only by prescription in the UK were available without prescription in Egypt (Sallam et al., 2009). Sales of psychotropic medications in Lebanon also increased during and after periods of conflict (Solberg, 2008), so people in some countries may self-medicate to cope with the psychological effects of invasion, warfare, conflict or political instability.

Differences in analgesic use between countries can also reflect differences in attitudes and beliefs. For example, Belgian women were six times more likely than Dutch women to use analgesics during labour and childbirth. This was attributed to differences in attitudes to pain and analgesics, reflecting differences between the Belgian medical model of maternity care and the Dutch midwifery model (Christaens et al., 2010). Beliefs about medication may be important mediators of socio-cultural factors like analgesic availability and healthcare provision, for they have been shown to differ between people from different cultural backgrounds (Horne et al., 2004) and to influence medication adherence (Horne & Weinman, 1999).

Interventions to reduce analgesic overuse and dependence should therefore target culturally relevant attitudes and beliefs. However, research on cultural influences on pain-related attitudes and behaviours has mainly employed clinical samples, so research is needed with general population samples in multiple countries. One review included 15 studies in France, nine in

Germany, and five each in the UK, Norway, Sweden and Finland, but very few studies with comparable data from more than one country (Casati et al., 2012).

Comparative international studies are necessarily complex because analgesic use and misuse are influenced by socio-cultural factors that operate at the level of the country as well as by attitudes and behaviours that operate at the level of the individual. The effects of such factors and the potential mediation of socio-cultural factors by individual factors can vary from country to country. Studies of this kind therefore need to make broad comparisons between countries but also investigate influences on analgesic use country-by-country. It is important, however, that the outcome variable is meaningful in each country. Analgesic 'misuse', 'overuse' or 'abuse' are problematic for this purpose, because socio-cultural influences mean that their definitions vary from country to country. For that reason the present study focused on analgesic dependence.

'Substance dependence' was replaced as a diagnostic category in DSM-5 by 'substance use disorder,' but the DSM-5 criteria for substance use disorder include all seven DSM-IV-TR criteria for substance dependence, so dependence is still an important component of substance use disorder (American Psychiatric Association, 2000, 2013). Analgesic dependence develops in a process involving changes in beliefs, attitudes and behaviours, and can be measured on a continuum; the Leeds Dependence Questionnaire (LDQ) measures the 'graded severity of psychological dependence' (Raistrick et al., 1994).

Analgesic dependence is therefore clinically meaningful and may also be an important precursor of more harmful analgesic use. Also, because it develops in a process, dependence should be amenable to change by interventions targeting key aspects of its development, such as specific beliefs and attitudes, so it is a worthwhile target for interventions. The aims of the present study were therefore to assess beliefs and attitudes as influences on analgesic dependence among analgesic users in the general populations of several different countries that were selected to include both developed and developing countries in multiple continents with varying degrees of availability of analgesics because of differences in legal restrictions.

Methods

The study comprised online questionnaire surveys in: 1) the UK, 2) the USA, 3) Australia, 4) Germany, 5) Egypt and 6) China, Macau and Hong Kong. Online surveys can be used to collect data from otherwise hard-to-reach populations while maintaining quality (Andrews et al., 2003; Ramsey et al., 2016). For example, one study found no differences in reliability and validity between online and paper-based questionnaires (Ritter et al., 2004).

Participants

The participants were 1,283 members of the general population who had pain and used analgesics in the previous month. The inclusion criteria were being at least 18 years old, having pain in the last month, using analgesics in the last month, living in the designated countries, and being able to read English/German/Arabic/Mandarin Chinese well enough to complete the questionnaires.

Translation of materials

Arabic, German and Mandarin Chinese versions of the survey materials were produced using a translation and back-translation procedure undertaken by native speakers of each language who were bilingual with English as their second language, following recommendations for translating research instruments (Cha et al., 2007; Van de Vijver & Hambleton, 1996). The materials were translated from English to Arabic, German and Mandarin by two translators for each language who worked independently. Any differences between the translations were resolved in discussion. The

agreed translation was back-translated to English by another two independent translators, and any differences were again resolved in discussion. The back-translations were then checked for accuracy by the authors.

The translators also advised about cultural sensitivity, and a small number of items were reworded or omitted on their advice. For example, ethnic origin was not recorded for the Germany survey because the translators advised that ethnicity is a sensitive topic in Germany. The Arabic, German and Mandarin translations of the main measures are available from the authors on request.

Measures

Participants reported their gender, age and marital status, and also how religious they felt, using a 5-point scale from 1 (not at all religious) to 5 (extremely religious), and whether they felt financially 'a little or a lot poorer than most', 'about the same as most', or 'a little or a lot richer than most', as in previous research (Ghandour et al., 2012).

The items about pain were derived from the Brief Pain Inventory (Cleeland & Ryan, 1994). Participants reported how long they had experienced pain and how many days they had pain in the last month. They rated their pain intensity in the last month 'at its worst', 'at its least', 'on average' and 'right now', with four 11-point scales ranging from 'no pain' (0) to 'pain as bad as you can imagine' (10)**.** The mean of the four ratings was the measure of pain intensity. This means that the measure of pain intensity was a composite of how participants' pain was in four ways – at its worst, at its least etc. – all focusing on pain in the last month. This composite is an alternative to using the single rating of pain 'at its worst' as the measure of pain intensity (Cleeland & Ryan, 1994). The composite score might understate pain intensity compared with the single rating of pain 'at its worst', but it has better reliability and validity (Jensen et al., 1993; 1999), and has been used in many other recent studies of chronic pain (eg., Lentz et al., 2018; Wilson et al., 2019).

Participants reported how many days they used analgesics in the last month; whether they used prescribed or over-the-counter analgesics, or both; and rated whether they 'never' (coded 0), 'sometimes' (1), 'usually' (2) or 'always' (3) used analgesics at higher doses than recommended, for longer than recommended, and when they were not in pain. The mean of the ratings for using analgesics at higher doses and for longer than recommended was used as a measure of analgesic overuse, as in previous research (Rosser et al., 2011). The rating for using analgesics when not in pain was used as a measure of analgesic abuse. Participants also indicated how easy it was for them to get strong painkillers without prescription, using a 5-point scale from 1 (probably impossible) to 5 (very easy).

Analgesic dependence was measured using the LDQ, a brief self-report measure of the graded severity of psychological dependence (Raistrick et al., 1994). There are 10 items based on ICD-10 and DSM-IV criteria for substance dependence, each with 4-point response scales labelled 'never' (0), 'sometimes' (1), 'often' (2) and 'nearly always' (3). A single score is computed as the total across the 10 items. The scale is widely used with good reliability and validity (Galeki et al., 2016; Kelly et al., 2010; Raistrick et al., 1994). We used a previously adapted version in which the words 'drink or drugs' in each item are replaced with 'painkillers' (e.g. 'do you find yourself thinking about when you will next be able to take painkillers?') (Elander et al., 2014).

Participants also completed the Survey of Pain Attitudes-Brief (SOPA-B), the Holistic, Complementary and Alternative Medicine Questionnaire (HCAMQ), the Self-Medicating Scale (SMS), and the Pain Medication Attitudes Questionnaire (PMAQ). The meanings of the constructs represented by each of the scales are summarised in table 1.

Table 1. Meanings of the constructs measured by the study scales

Construct	Definition
LDQ	The graded severity of psychological dependence
SOPA-B	
Solicitude	Needing more tender loving care and wanting better treatment from family when in pain
Emotion	Belief that depression and anxiety increase feelings of pain
Medical Cure	Belief in a medical cure for pain
Control	Feeling that one can influence how much pain one feels
Harm	Belief that pain indicates damage and that activity can cause harm
Disability	Belief that pain prevents one from leading a physically active life
Medication	Belief in the effectiveness of medications to manage pain
HCAMQ	
HH	Beliefs about the influence of emotions, stress, thoughts and behaviours on health
CAM	Beliefs about the scientific validity of complementary and alternative medicine
SMS	
Reluctance	Belief in self-medicating only when the symptoms experienced are severe
Don't Think Twice	Belief in not hesitating to self-medicate
Run its Course	Belief in letting the body deal with the ailment naturally rather than take medication to cure it
PMAQ	
Addiction	Feeling concerned about becoming addicted to pain medication
Need	Feeling dependent on and being unwilling to reduce pain medication
Scrutiny	Feeling embarrassed by and worrying what others think about using pain medication
Side-effects	Worrying about damage caused by pain medication and finding side effects hard to put up with
Tolerance	Worrying that pain medication will stop working to help with the pain
Mistrust of Doctors	Not being satisfied or confident about the doctor's management of pain
Withdrawal	Worrying that stopping taking pain medication will cause harm or illness

LDQ=Leeds Dependence Questionnaire; SOPA-B=Survey of Pain Attitudes-Brief; HCAMQ=Holistic, Complementary and Alternative Medicine Questionnaire; HH= Holistic Health; CAM=Complementary and Alternative Medicine; SMS=Self-Medicating Scale; PMAQ=Pain Medication Attitudes Questionnaire.

The SOPA-B is a 30-item self-report measure of attitudes to pain using 5-point response scales from 'very untrue' (0) to 'very true' (4). Scores are computed as means across items for seven scales: Solicitude, Emotion, Medical Cure, Control, Harm, Disability, and Medication. The SOPA-B had good reliability and validity, and was recommended for use where very focal belief dimensions were required, for the scales are narrowly focused on specific components of what are broader constructs in other SOPA versions (Jensen et al., 2000; Tait & Chibnall, 1997). Participants in the UK and Egypt completed the 30-item SOPA-B (Tait & Chibnall, 1997) and those in all other countries completed a 14-item version derived directly from the 30-item SOPA-B (Said, 2017).

The HCAMQ is an 11-item scale measuring attitudes and beliefs towards holistic health and complementary and alternative medicine with 6-point scales from 'strongly disagree' (1) to 'strongly agree' (6). Scores are summed across items to give scores for a Holistic Health subscale (HH) and a

Complementary and Alternative Medicine subscale (CAM), as well as a total score. Test-retest reliability and internal consistency were good (Hyland et al., 2003).

The SMS is a 9-item measure of beliefs about self-medication with 5-point scales from 'strongly disagree' (1) to 'strongly agree' (5). Scores are summed across items for three scales: 'Reluctance', 'Don't Think Twice' and 'Run its Course', which had good reliability and validity (James & French, 2008).

The PMAQ is a 47-item self-report measure of attitudes to pain medication with 6-point scales from 'never true' (0) to 'always true' (5). Scale scores are computed as means across items making up seven scales: Addiction, Need, Scrutiny, Side-effects, Tolerance, Mistrust of Doctors, and Withdrawal. Reliability and validity were good (McCracken et al., 2006; Rosser et al., 2011). Participants in the UK and Egypt completed the 47-item PMAQ (McCracken et al., 2006) and those in all other countries completed a 14-item version (Elander et al., 2017).

Procedure

The study protocol was approved by the University of Derby Psychology Research Ethics Committee. The surveys were all web-based general population surveys, each restricted to residents of the countries concerned. The surveys in the UK, USA and Australia were restricted to English speaking residents of those countries, and those in Egypt, Germany and China/Macau/Hong Kong were restricted to Arabic-speaking, German-speaking and Mandarin Chinese-speaking residents respectively.

For each survey, participants were recruited by posting brief invitation messages on relevant online discussion and support forums, for example http://painsupport.co.uk, www.chronicpainsite.com, and www.chronicpainaustralia.org.au. The surveys gave further information including inclusion criteria, and participants confirmed consent before proceeding. In recognition of the time and effort involved, participants were offered entry to a prize draw for each survey for a gift voucher worth £50, $100, AU$100, €80, 70 Egyptian Pounds, and 700 Yen. The surveys were all anonymous, but each participant had a unique identifying code, and these were compared between surveys to ensure no individuals participated more than once. We also conducted a data audit and screening exercise before the data were analysed, to review participants' demographic and other information to ensure that each described a genuine case and that there were no duplicate cases or instances where one individual had completed the survey more than once.

Analytic strategy

The six samples were compared using Chi Squared tests and one way analyses of variance. Hierarchical multiple linear regression analyses with analgesic dependence (LDQ scores) as the dependent variables were then conducted separately for each country. Predictor variables that were significantly correlated with analgesic dependence were added to the models using the stepwise method within each of four blocks: 1) demographic and clinical factors; 2) pain duration, frequency and intensity; 3) analgesic use, overuse and abuse; 4) beliefs and attitudes. The criteria for entry and removal were $p < 0.05$ and $p > 0.10$ respectively.

Where regression coefficients were substantially reduced when another predictor was added to the model, we conducted Sobel tests (Sobel, 1982) using Preacher and Hayes's (2004) SPSS macro to test for mediation, which occurs when a mediating variable "accounts for the relationship between the predictor and the criterion" (Baron & Kenny, 1986, p. 1176).

Table 2. Demographic and clinical details for participants in each country

	UK (a)	USA (b)	Australia (c)	Germany (d)	Egypt (e)	China/Macau/ Hong Kong (f)	Total	X^2 or F
N	295	138	94	226	420	110	1,283	
Mean (SD) age	41.2 (12.3)[b,c,d,e,f]	47.37 (11.4)[a,d,e,f]	46.6 (14.0)[a,d,e,f]	30.6 (10.7)[a,b,c,e]	35.4 (12.7)[a,b,c,d,f]	31.0 (10.6)[a,b,c,e]	37.6 (13.4)	F= 58.3***
Female	225 (86.4%)	114 (82.6%)	74 (78.7%)	183 (81.0%)	195 (46.4%)	68 (61.8%)	889 (69.3%)	X^2=177***
Married/cohabiting	197 (66.8%)	114 (82.6%)	57 (60.6%)	124 (54.9%)	240 (57.3%)	43 (39.1%)	775 (60.5%)	X^2=59.0***
Mean (SD) religiousness[1]	2.09 (1.20)[b,e]	2.87 (1.32)[a,c,d,e]	1.95 (1.16)[b,e]	2.24 (1.17)[b,e]	3.44 (1.08)[a,b,c,d,f]	2.44 (1.40)[e]	2.66 (1.32)	F=65.1***
Perceived financial status								
Poorer than most	91 (30.8%)	36 (26.1%)	34 (36.2%)	83 (36.7%)	128 (30.5%)	9 (13.0%)	381 (30.7%)	X^2=35.4***
Same as most	172 (58.3%)	84 (60.9%)	50 (53.2%)	128 (56.6%)	229 (54.5%)	58 (84.1%)	721 (58.1%)	
Richer than most	32 (10.8%)	18 (13.0%)	10 (10.6%)	15 (6.6%)	63 (15.0%)	2 (2.9%)	140 (11.3%)	
Pain > 12 months	259 (87.8%)	124 (89.9%)	82 (87.2%)	118 (52.2%)	22 (5.3%)	26 (23.6%)	631 (49.3%)	X^2=673***
Diagnosed pain condition	254 (86.1%)	131 (94.9%)	84 (89.4%)	114 (50.4%)	271 (64.8%)	34 (30.9%)	888 (69.3%)	X^2=218***
Mean (SD) pain frequency[2]	24.2 (9.88)[c,d,e,f]	26.67 (7.60)[d,e,f]	27.78 (6.84)[a,d,e,f]	12.64 (10.57)[a,b,c,e,f]	3.89 (3.22)[a,b,c,d]	5.81 (6.76)[a,b,c,d]	14.46 (12.39)	F=410***
Mean (SD) Pain intensity[3]	5.33 (1.88)[d,e,f]	5.11 (1.54)[d,f]	5.15 (1.65)[d,f]	3.67 (1.49)[a,b,c,e,f]	4.80 (1.89)[a,d,f]	2.53 (1.47)[a,b,c,d,e]	4.59 (1.93)	F=60.52***
Mean (SD) analgesic use[2]	21.79 (11.44)[c,d,e,f]	23.53 (10.29)[d,e,f]	25.83 (9.36)[a,d,e,f]	8.06 (9.77)[a,b,c,e,f]	3.37 (3.71)[a,b,c,d]	2.16 (3.50)[a,b,c,d]	12.13 (12.48)	F=313***
Mean (SD) ease to obtain analgesics[4]	2.11 (1.22)[d,e]	1.97 (1.15)[d,e]	1.78 (1.15)[d,e]	2.65 (1.27)[a,b,c,e]	3.55 (1.09)[a,b,c,d,f]	2.21 (1.36)[e]	2.64 (1.36)	F=82.5***
Prescription analgesics	239 (81.0%)	125 (90.6%)	81 (86.2%)	95 (42.0%)	264 (63.8%)	40 (36.4%)	844 (66.1%)	X^2=186***
Analgesic overuse								
At least sometimes[5]	129 (43.7%)	42 (30.4%)	50 (53.2%)	53 (23.5%)	378 (90.0%)	21 (19.1%)	673 (52.5%)	X^2=399***
At least usually[5]	47 (15.9%)	8 (5.8%)	14 (14.9%)	10 (4.4%)	234 (55.7%)	4 (3.6%)	317 (24.7%)	X^2=337***
Analgesic abuse								
At least sometimes	27 (9.2%)	7 (5.1%)	17 (18.1%)	11 (4.9%)	338 (80.5%)	15 (13.6%)	415 (32.4%)	X^2=668***
At least usually	6 (2.0%)	3 (2.2%)	5 (5.3%)	0 (0%)	192 (45.7%)	3 (2.7%)	209 (16.3%)	X^2=398***

1) 1-5 scale, higher scores = more religious; 2) Number of days in the last month; 3) 0-10 scale, higher scores=more intense pain; 4) 1-5 scale, higher scores=greater ease; 5) either at higher doses or for longer than recommended; *** p <= 0.001; Superscript letters show country means that differ significantly (p<=0.05) by Sheffe post-hoc multiple comparison tests.

Results

Table 2 shows participant demographic and clinical details. Participants in the USA and Australia were older and those in Germany and China/Macau/Hong Kong were younger than in other countries. The proportions of females were highest in the UK and lowest in Egypt. The proportions married or cohabiting were highest in the USA and lowest in China/Macau/Hong Kong. Religiousness ratings were highest in Egypt and lowest in Australia. In every country, the majority rated their financial status as 'about the same as most', but that majority was greatest in China/Macau/Hong Kong.

The proportions with pain longer than 12 months, and with diagnosed pain conditions and prescribed pain medications, were higher in the UK, USA and Australia, and lower in Germany, Egypt and China/Macau/Hong Kong. Pain frequency and intensity, and analgesic use frequency, were also higher in the UK, USA and Australia, and lower in Germany, Egypt and China/Macau/Hong Kong.

However, ease of obtaining strong analgesics was higher in Egypt than all other countries, and the proportions with analgesic misuse and abuse were also highest in Egypt.

Table 3 shows mean questionnaire scores. For SOPA scales, Solicitude scores were higher in China/Macau/Hong Kong and Egypt than all other countries. Emotion scores were lower in Germany than all other countries. Medical Cure scores were lower in China/Macau/Hong Kong than all other countries except Egypt. Control scores were higher in Egypt than all other countries except China/Macau/Hong Kong. Harm scores were lower in Germany than all other countries. Disability scores were higher in the UK, USA and Australia, and lower in Germany, than in other countries. Medication scores were higher in the UK and USA and lower in Germany and China/Macau/Hong Kong than in other countries.

For HCAMQ scales, Holistic Health and total HCAMQ scores were higher in Egypt than all other countries. CAM scores and total HCAMQ scores were lower in China/Macau/Hong Kong than all other countries.

For SMS scales, Reluctance scores were lower in Egypt than all other countries except Australia. Don't Think Twice scores were higher in Egypt than all other countries except the UK and Australia, and lower in Germany than all other countries. Run its Course scores were higher in Egypt and China/Macau/Hong Kong than all other countries, and lower in UK and USA than all other countries except Australia.

For PMAQ scales, Addiction scores were higher in Egypt than all other countries. Need scores were higher in Egypt than all other countries except USA, and lower in China/Macau/Hong Kong than all other countries except Germany. Scrutiny scores were higher in Egypt than all other countries, and lower in Germany than all other countries except China/Macau/Hong Kong. Side-effects, Tolerance and Withdrawal scores were higher in Egypt and lower in Germany than all other countries. Mistrust scores were higher in Egypt, UK and China/Macau/Hong Kong than in USA or Australia. Across the types of concern represented by PMAQ scales, therefore, Egypt had the highest and Germany the lowest scores. For analgesic dependence (LDQ), scores were also higher in Egypt than any other country, and lower in Germany and China/Macau/Hong Kong than any other country.

The differences between countries therefore showed that pain medication attitudes, rates of analgesic misuse and abuse, and levels of analgesic dependence were all highest in Egypt, but pain frequency and intensity and analgesic use frequency were all higher in the UK, USA and Australia.

Table 3. Mean (SD) scale scores for participants in each country

	UK (a)	USA (b)	Australia (c)	Germany (d)	Egypt (e)	China/Macau/ Hong Kong (f)	Total	F
SOPA scales								
Solicitude	1.81 (1.18)^{e,f}	1.96 (1.16)^{d,e,f}	1.95 (1.09)^{e,f}	1.58 (1.08)^{b,e,f}	2.43 (0.91)^{a,b,c,d,f}	2.81 (0.94)^{a,b,c,d,e}	2.09 (1.12)	34.8***
Emotion	2.38 (1.19)^{d}	2.53 (1.15)^{d}	2.48 (1.21)^{d}	1.87 (1.28)^{a,b,c,e,f}	2.40 (1.02)^{d}	2.45 (0.97)^{d}	2.33 (1.15)	9.31***
Medical Cure	1.88 (1.18)^{f}	2.00 (1.28)^{e,f}	2.26 (1.17)^{d,e,f}	1.78 (1.19)^{c,f}	1.63 (0.92)^{b,c}	1.26 (0.99)^{a,b,c,d}	1.77 (1.12)	11.7***
Control	1.58 (1.03)^{e,f}	1.58 (1.07)^{e,f}	1.76 (1.19)^{e}	1.72 (1.08)^{e}	2.40 (0.92)^{a,b,c,d}	2.09 (0.93)^{a,b,}	1.93 (1.07)	31.4***
Harm	2.23 (1.04)^{d}	2.48 (0.94)^{d,e}	2.42 (1.03)^{d,e}	1.51 (1.11)^{a,b,c,e,f}	2.02 (0.63)^{b,c,d,f}	2.50 (0.72)^{d,e}	2.10 (0.96)	32.7***
Disability	2.46 (1.20)^{d,e,f}	2.59 (1.06)^{d,e,f}	2.52 (1.02)^{d,e,f}	1.24 (1.12)^{a,b,c,e,f}	2.04 (0.57)^{a,b,c,d}	1.81 (0.82)^{a,b,c,d}	2.07 (1.05)	58.0***
Medication	2.81 (0.93)^{d,e,f}	2.95 (1.07)^{d,e,f}	2.59 (1.01)^{d,f}	1.92 (1.14)^{a,b,c,e,f}	2.41 (1.05)^{a,b,d,f}	1.52 (0.92)^{a,b,c,d,e}	2.41 (1.11)	43.7***
HCAMQ scales								
Holistic Health	10.78 (3.90)^{e}	10.38 (3.15)^{e}	10.50 (3.34)^{e}	10.20 (3.27)^{e}	14.86 (5.65)^{a,b,c,d,f}	9.26 (3.47)^{e}	11.82 (4.83)	63.6***
CAM	21.80 (5.81)^{d,f}	21.02 (4.24)^{f}	21.60 (4.16)^{f}	20.29 (3.71)^{a,e,f}	22.17 (2.95)^{d,f}	17.10 (3.94)^{a,b,c,d,e}	21.15 (4.42)	29.0***
Total	32.58 (7.22)^{d,e,f}	31.41 (5.42)^{e,f}	32.10 (5.44)^{e,f}	30.48 (5.30)^{a,e,f}	37.02 (3.92)^{a,b,c,d,f}	26.36 (6.00)^{a,b,c,d,e}	32.97 (6.39)	89.4 ***
Self-medicating Scale								
Reluctance	11.35 (3.48)^{e}	11.06 (3.39)^{d,e}	10.97 (3.28)	12.27 (3.27)^{b,e}	9.87 (3.31)^{a,b,d,f}	12.11 (2.25)^{e}	11.03 (3.39)	20.0***
Don't Think Twice	9.81 (3.32)^{d}	8.83 (2.97)^{d,e}	9.31 (3.34)^{d}	7.04 (2.92)^{a,b,c,e,f}	10.23 (3.03)^{b,d,f}	8.97 (2.95)^{d,e}	9.25 (3.28)	34.1***
Run its Course	7.65 (2.97)^{d,e,f}	7.51 (2.86)^{d,e,f}	7.76 (2.71)^{e,f}	8.62 (2.98)^{a,b,e,f}	10.21 (3.01)^{a,b,c,d}	9.75 (2.27)^{a,b,c,d}	8.83 (3.11)	39.4***
PMAQ								
Addiction	1.53 (1.44)^{e,f}	1.41 (1.13)^{e,f}	1.60 (1.45)^{e}	1.45 (1.44)^{e,f}	2.95 (1.20)^{a,b,c,d,f}	2.22 (1.40)^{a,b,d,e}	2.03 (1.49)	65.3***
Need	2.32 (1.64)^{d,e,f}	2.58 (1.48)^{d,f}	2.30 (1.48)^{d,e,f}	1.21 (1.42)^{a,b,c,e}	2.91 (1.13)^{a,c,d,f}	1.00 (1.12)^{a,b,c,e}	2.23 (1.54)	64.9***
Scrutiny	1.14 (1.44)^{b,d,e}	1.61 (1.59)^{a,d,e,f}	1.58 (1.54)^{d,e,f}	0.60 (1.00)^{a,b,c,e}	2.91 (1.16)^{a,b,c,d,f}	0.84 (1.00)^{b,c,e}	1.68 (1.57)	131.9***
Side-effects	2.05 (1.36)^{d,e}	1.90 (1.18)^{d,e}	2.19 (1.17)^{d,e}	1.45 (1.42)^{a,b,c,e,f}	2.91 (1.16)^{a,b,c,d,f}	2.31 (1.26)^{d,e}	2.26 (1.37)	49.6***
Tolerance	2.25 (1.62)^{d,e}	2.00 (1.22)^{d,e}	2.19 (1.54)^{d,e}	0.98 (1.33)^{a,b,c,e,f}	2.94 (1.19)^{a,b,c,d,f}	1.79 (1.23)^{d,e}	2.18 (1.51)	64.4***
Mistrust	2.74 (1.60)^{b,c,d}	1.74 (1.40)^{a,e,f}	1.78 (1.49)^{a,e,f}	2.10 (1.49)^{a,e}	2.99 (1.18)^{b,c,d}	2.60 (1.25)^{b,c}	2.52 (1.47)	29.1***
Withdrawal	1.90 (1.58)^{d,e,}f	1.71 (1.52)^{d,e}	1.45 (1.52)^{d,e}	0.64 (1.21)^{a,b,c,e,f}	2.95 (1.22)^{a,b,c,d,f}	1.20 (1.27)^{a,d,e}	1.91 (1.60)	95.3***
Dependence (LDQ)	10.18 (5.75)^{b,c,d,e,f}	7.57 (5.22)^{a,c,d,e,f}	10.25 (5.98)^{b,d,e,f}	5.00 (4.17)^{a,b,c,e}	16.53 (6.10)^{a,b,c,d,f}	4.61 (4.42)^{a,b,c,e}	10.59 (7.15)	180.4***

1) SOPA=Survey of Pain Attitudes; HCAMQ= Holistic, Complementary and Alternative Medicine Questionnaire; CAM= Complementary and Alternative Medicine; PMAQ= Pain Medication Attitudes Questionnaire; LDQ=Leeds Dependence Questionnaire; *** p <= 0.001; Superscript letters show country means that differ significantly (p<=0.05) by Sheffe post-hoc multiple comparison tests.

Analgesic dependence was correlated significantly with pain frequency and analgesic frequency in every country except Egypt; the correlations with pain frequency ranged from 0.27 (p=0.009) in Australia to 0.45 (p<0.001) in Germany, and the correlations with analgesic frequency ranged from 0.44 (p<0.001) in Australia to 0.68 (p<0.001) in Germany. Analgesic dependence was also significantly correlated with the SOPA Medication scale, and the PMAQ Addiction, Need, Tolerance and Withdrawal scales in every country, with coefficients ranging from 0.16 (p=0.001) for Tolerance and Withdrawal in Egypt to 0.69 (p<0.001) for Need in China/Macau/Hong Kong.

Table 4 shows the regression analysis for the UK. Over half the variance (0.54) in analgesic dependence was accounted for. Eleven variables were predictive when first added to the model, but only analgesic frequency and four belief and attitude scales were independent predictors in the final model. Age and financial status became non-significant when pain frequency was added to the model and religiousness became non-significant when diagnosis was added. Pain frequency mediated the effects of age (Sobel = 0.054, 95% CIs 0.028 to 0.079, p < 0.0001) and financial status (Sobel = -0.928, 95% CIs -1.406 to -0.450, p = 0.0001), but diagnosis did not mediate religiousness.

Pain frequency and intensity became non-significant when analgesic frequency was added, and analgesic frequency mediated the effects of pain frequency (Sobel = 0.240, 95% CIs 0.172 to 0.308, p < 0.0001) and intensity (Sobel = 0.777, 95% CIs 0.542 to 1.012, p < 0.0001). Diagnosis remained significant until Need was added, and Need mediated the effect of diagnosis (Sobel = 2.590, 95% CIs 1.471 to 3.708, p < 0.0001). Analgesic frequency remained significant but was substantially reduced when Need was added, and Need mediated the effect of analgesic frequency (Sobel = 0.978, 95% CIs 0.0664 to 0.1291, p < 0.0001). Need was the most significant predictor in the final model, but Tolerance, Side-effects and Control also had significant independent effects.

Table 4. Summary of regression analysis of analgesic dependence in the UK

Block and predictor variable	R^2	Adj. R^2	ΔR^2	Entry Beta	Final Beta
1. Demographic factors	0.049	0.039	0.049*		
Religiousness				0.137*	0.034
Financial status				-0.127*	-0.015
Age				0.118*	-0.086
2. Pain	0.217	0.201	0.168***		
Pain frequency				0.367***	-0.047
Diagnosed pain condition				0.214***	0.032
Pain intensity				0.173*	0.049
3. Analgesic use	0.318	0.302	0.101***		
Analgesic frequency				0.491***	0.279***
4. Beliefs and attitudes	0.540	0.522	0.221***		
Need				0.466***	0.399***
Tolerance				0.224***	0.181**
Control				0.121*	0.115*
Side-effects				0.111*	0.111*

Dependent variable = analgesic dependence (Leeds Dependence Questionnaire score); R^2= proportions of variance accounted for; ΔR^2 = change in R^2; Beta weights = standardized regression coefficients. Variables were added to the model using the stepwise method in each block. The criteria for entry and removal were $p < 0.05$ and $p > 0.10$ respectively. Only predictor variables that were entered are shown in the table. * p <= .05; ** p <= .01; *** p <= .001.

Table 5 shows the regression analysis for the USA. Just under half the variance (0.49) was accounted for and four belief and attitude scores were independent predictors in the final model. As in the UK, pain frequency became non-significant when analgesic frequency was added, and analgesic frequency mediated the effect of pain frequency (Sobel = 0.216, 95% CIs 0.119 to 0.312, p < 0.0001).

The effects of analgesic frequency and analgesic overuse were reduced but remained significant when Withdrawal and Run its Course were added, but analgesic frequency became non-significant when Need and then Addiction were added, whereas analgesic overuse remained significant in the final model. Withdrawal, Need and Run its Course all mediated the effect of analgesic frequency (Withdrawal: Sobel = 0.083, 95% CIs 0.041 to 0.126, p = 0.0002; Run its Course: Sobel = 0.038, 95% CIs 0.007 to 0.071, p = 0.016; Need: Sobel = 0.090, 95% CIs 0.042 to 0.139, p = 0.0003), but Addiction did not, and none of those scores mediated the effects of analgesic overuse.

Table 5. Summary of regression analysis of analgesic dependence in the USA.

Block and predictor variable	R^2	Adj. R^2	ΔR^2	Entry Beta	Final Beta
1. Demographic factors					
No variables entered					
2. Pain	0.079	0.072	0.079***		
Pain frequency				0.280***	0.010
3. Analgesic use	0.258	0.242	0.179***		
Analgesic frequency				0.489***	0.178
Analgesic overuse				0.186*	0.129*
4. Beliefs and attitudes	0.492	0.465	0.234***		
Withdrawal				0.403***	0.271***
Run its Course				-0.227***	-0.204**
Need				0.232**	0.233**
Addiction				0.135*	0.135*

Dependent variable = analgesic dependence (Leeds Dependence Questionnaire score); R^2= proportion of variance accounted for; ΔR^2 = change in R^2; Beta weights = standardized regression coefficients. Variables were added to the model using the stepwise method in each block. The criteria for entry and removal were $p < 0.05$ and $p > 0.10$ respectively. Only predictor variables that were entered are shown in the table. * p <= .05; ** p <= .01; *** p <= .001.

Table 6 shows the regression analysis for Australia. Just under half the variance (0.496) was accounted for and analgesic frequency, Need and Tolerance were independent predictors in the final model. Pain frequency became non-significant when analgesic frequency was added, and analgesic frequency mediated the effect of pain frequency (Sobel = 0.286, 95% CIs 0.120 to 0.453, p = 0.0007). Analgesic frequency and analgesic abuse were both substantially reduced when Need was added. Need mediated the effect of analgesic frequency (Sobel = 0.178, 95% CIs 0.092 to 0.264, p < 0.0001) but not that of analgesic abuse.

Table 7 shows the regression analysis for Germany. Over half the variance (0.57) was accounted for, and analgesic frequency, Need and Withdrawal were independent predictors in the final model. Age was initially predictive, but both age and pain intensity became non-significant when analgesic frequency was added. Analgesic frequency mediated the effects of age (Sobel = 0.136, 95% CIs -0.099 to 0.172, p < 0.0001) and pain intensity (Sobel = 1.092, 95% CIs 0.811 to 1.373, p < 0.0001).

Pain duration became non-significant when Need was added, and analgesic frequency was substantially reduced when first Need then Withdrawal were added. Need mediated the effects of pain duration (Sobel = 0.500, 95% CIs 0.336 to 0.664, p < 0.0001) and analgesic frequency (Sobel =

0.115, 95% CIs 0.079 to 0.151, p < 0.0001). Withdrawal also mediated the effects of pain duration (Sobel = 0.343, 95% CIs 0.194 to 0.493, p < 0.0001) and analgesic frequency (Sobel = 0.100, 95% CIs 0.061 to 0.139, p < 0.0001).

Table 6. Summary of regression analysis of analgesic dependence in Australia.

Block and predictor variable	R^2	Adj. R^2	ΔR^2	Entry Beta	Final Beta
1. Demographic factors					
No variables entered					
2. Pain	0.073	0.062	0.073**		
Pain frequency				0.269***	-0.146
3. Analgesic use	0.228	0.202	0.155***		
Analgesic frequency				0.477***	0.278*
Analgesic abuse				0.192*	0.084
4. Beliefs and attitudes	0.496	0.467	0.268***		
Need				0.545***	0.387***
Tolerance				0.282**	0.282**

Dependent variable = analgesic dependence (Leeds Dependence Questionnaire score); R^2= proportions of variance accounted for; ΔR^2 = change in R^2; Beta weights = standardized regression coefficients. Variables were added to the model using the stepwise method in each block. The criteria for entry and removal were $p < 0.05$ and $p > 0.10$ respectively. Only predictor variables that were entered are shown in the table. * p <= .05; ** p <= .01; *** p <= .001.

Table 7. Summary of regression analysis of analgesic dependence in Germany.

Block and predictor variable	R^2	Adj. R^2	ΔR^2	Entry Beta	Final Beta
1. Demographic factors	0.241	0.238	0.241***		
Age				0.491***	0.039
2. Pain	0.340	0.331	0.098***		
Pain intensity				0.323***	-0.013
Pain duration				0.138*	0.060
3. Analgesic use	0.476	0.466	0.136***		
Analgesic frequency				0.534***	0.288***
4. Beliefs and attitudes	0.573	0.561	0.097***		
Need				0.397***	0.329***
Withdrawal				0.191**	0.191**

Dependent variable = analgesic dependence (Leeds Dependence Questionnaire score); R^2= proportions of variance accounted for; ΔR^2 = change in R^2; Beta weights = standardized regression coefficients. Variables were added to the model using the stepwise method in each block. The criteria for entry and removal were $p < 0.05$ and $p > 0.10$ respectively. Only predictor variables that were entered are shown in the table. * p <= .05; ** p <= .01; *** p <= .001.

Table 8 shows the regression analysis for Egypt. Very little variance in analgesic dependence was accounted for (0.129), but pain duration, analgesic overuse, Emotion and Solicitude were significant predictors in the final model. The effect of pain duration was negative, so that pain with more recent onset was predictive of dependence, and the effects of pain duration and analgesic overuse remained significant when other measures were added. The negative effect of pain duration seems counter-intuitive, but one interpretation may that the easy availability of strong analgesics in Egypt means that people tend to self-medicate as an initial response to pain whereas people with more long-standing pain are more likely to have seen a doctor or developed other pain coping strategies.

Table 8. Summary of regression analysis of analgesic dependence in Egypt

Block and predictor variable	R^2	Adj. R^2	ΔR^2	Entry Beta	Final Beta
1. Demographic factors	0.010	0.007	0.010*		
Age				0.098*	0.072
2. Pain	0.028	0.023	0.018**		
Pain duration				-0.135**	-0.127**
3. Analgesic use	0.037	0.030	0.009*		
Analgesic overuse				0.097*	0.093*
4. Beliefs and attitudes	0.129	0.118	0.092**		
Emotion				0.273***	0.188**
Solicitude				0.160*	0.160**

Dependent variable = analgesic dependence (Leeds Dependence Questionnaire score); R^2= proportions of variance accounted for; ΔR^2 = change in R^2; Beta weights = standardized regression coefficients. Variables were added to the model using the stepwise method in each block. The criteria for entry and removal were $p < 0.05$ and $p > 0.10$ respectively. Only predictor variables that were entered are shown in the table. * p <= .05; ** p <= .01; *** p <= .001.

Table 9 shows the regression analysis for China/Macau/Hong Kong. Almost two-thirds of the variance (0.606) was accounted for. Age, pain intensity and Need were independent predictors in the final model. The effect of pain intensity was substantially reduced when analgesic abuse and Need were added, and analgesic abuse became non-significant when Need was added. Need mediated the effect of pain intensity (Sobel = 0.706, 95% CIs 0.341 to 1.071, p = 0.0002), but analgesic abuse did not mediate pain intensity, and Need did not mediate analgesic abuse.

Table 9. Summary of regression analysis of analgesic dependence in China/Macau/Hong Kong

Block and predictor variable	R^2	Adj. R^2	ΔR^2	Entry Beta	Final Beta
1. Demographic factors	0.226	0.214	0.226***		
Age				0.475***	0.333***
2. Pain	0.437	0.420	0.211***		
Pain intensity				0.460***	0.287***
3. Analgesic use	0.480	0.456	0.043*		
Analgesic abuse				0.213***	0.141
4. Beliefs and attitudes	0.606	0.581	0.125***		
Need				0.429***	0.429***

Dependent variable = analgesic dependence (Leeds Dependence Questionnaire score); R^2= proportions of variance accounted for; ΔR^2 = change in R^2; Beta weights = standardized regression coefficients. Variables were added to the model using the stepwise method in each block. The criteria for entry and removal were $p < 0.05$ and $p > 0.10$ respectively. Only predictor variables that were entered are shown in the table. * p <= .05; ** p <= .01; *** p <= .001.

Discussion

Frequency of analgesic use was consistently correlated with analgesic dependence and mediated the effects of pain frequency and intensity in the UK, USA, Australia and Germany. This resembles Elander et al.'s (2014) 'pathway A', in which greater pain leads to greater use of analgesics, which then leads to increased analgesic dependence. By contrast, analgesic overuse predicted dependence only in Egypt, and analgesic abuse was not predictive in any country. The

implication is that interventions to prevent analgesic dependence should focus on reducing people's frequency of analgesic use.

The attitudes measured by the PMAQ were also important predictors of dependence, especially the Need subscale, which was an independent predictor in every country except Egypt and mediated the effects of analgesic frequency in the UK, USA, Australia and Germany. The Tolerance subscale was also an independent predictor in the UK and Australia, and the Withdrawal subscale was an independent predictor in the USA and Germany, but the Addiction subscale was predictive only in the USA.

The Need, Tolerance and Withdrawal subscales all refer to physiological aspects of dependence, suggesting that concerns or fears about physiological dependence play an important role in people's feelings of dependence on analgesics. The fact that Need scores were a much stronger and more consistent predictor of analgesic dependence than behavioural factors like analgesic overuse and abuse shows that subjective, self-reported concerns about analgesic use are reliable indicators that could be used for screening or targeting. For example, simple questions based on the two Need items in the 14-item PMAQ might be useful in public health education initiatives to help people assess their risk of analgesic dependence, or to help guide health professionals in their assessments of patients' risk of analgesic dependence (for example, '*Would you be unwilling to reduce your pain medication*?' and '*Do you feel you depend on your pain medication*?')

There were considerable similarities between countries, especially the UK, USA, Australia and Germany, suggesting that those samples represented similar populations. However, there were also differences between countries. The proportions of variance in analgesic dependence that were accounted for in the regression analyses ranged from 61% in China to just 13% in Egypt, where the pattern of analgesic use seemed qualitatively different from other countries. The differences between countries highlight the complexity of investigating analgesic use internationally, and the present findings offer conclusions at different levels. For example, whereas analgesic frequency mediated the effects of pain frequency or intensity in the UK, USA, Australia and Germany, there were different influences and less clear processes in Egypt and China/Macau/Hong Kong. In those countries, more research is needed to understand influences on analgesic use.

In Egypt, participants had less pain and less frequent analgesic use, but more overuse, abuse and dependence, so this sample may include more people using analgesics for reasons other than pain, perhaps because access to strong analgesics was rated as easier in Egypt than all other countries. Analgesic overuse was a significant predictor of dependence only in Egypt, so the influences on dependence in Egypt may reflect Elander et al.'s (2014) 'pathway B', which involves factors that increase the risk of addiction irrespective of pain. Future research on analgesic use in Egypt and other countries in that region should perhaps therefore include measures of risk of addiction and 'aberrant' drug taking behaviour (Passik et al., 2008).

In Egypt, the SOPA scales Emotion and Solicitude rather than PMAQ scores were predictive of dependence. Emotion measures the extent to which feelings like anxiety and depression increase the pain people feel, and Solicitude measures how people value sympathy and consideration from others when they are in pain. This pattern suggests that analgesic dependence was influenced more by emotional and social factors in Egypt.

Participants in China/Macau/Hong Kong were similar in some ways to those in Egypt, with less chronic pain, less frequent and less intense pain, as well as fewer diagnosed pain conditions and fewer prescribed analgesics, but differed in having less analgesic overuse and abuse, and lower Need scores. Analgesic dependence was relatively well explained in China/Macau/Hong Kong, with 61% of the variance accounted for by greater age, more intense pain, and greater concerns about Need,

which mediated the effect of analgesic abuse. The effects of age were not mediated by other factors, so older people were more dependent for reasons not explained by other study measures.

There are some study limitations to consider. The questionnaire was relatively long, with a total of 74 items (123 for participants in the UK and Egypt who completed longer versions of the SOPA-B and PMAQ), which we estimate took participants 15-20 minutes to complete. This may have deterred some participants from completing the survey, although in fact there were very few people who began the survey but did not complete it (2 in the UK, 8 in the USA, 1 in Australia, 9 in Germany, 20 in Egypt, and 34 in China/Macau/Hong Kong).

Online survey methods have been shown to be valid and reliable (Andrews et al., 2003; Ramsey et al., 2016; Ritter et al., 2004), and may be an important strategy to enable people in diverse parts of the world to take part in international research. However, we can't rule out the possibility that online surveys risk under-representing poorer individuals in countries like Egypt, who may have less access to the internet, or that participation could have been inhibited by concerns about privacy protection in countries like China. Similarly, prize draws for values like those in the present study are very often used in online surveys (Göritz, 2006), and there is evidence that they increase response rates without affecting response quality or sample composition (Sánchez-Fernández et al., 2010). Again, however, we can't rule out the possibility that prize draws could affect responding differently in different countries, and they might be expected to have a greater impact in poorer countries.

Representativeness is a potential limitation because it is ultimately unknown what percentage of participants who learned about the survey chose to participate. However, it is inherent in all cross-cultural or comparative international research that different factors may affect responding in different countries, especially when countries are selected for data collection because they differ socially or economically.

It is also possible that despite the efforts we took, there were individuals who, in order to increase their chance of winning the prize draw, went to the trouble of using a different email address and a different computer in order to complete the survey more than once. We described earlier the steps we took to prevent and avoid this (see procedure), which included a careful data audit and identification of duplicate cases. Considering the targeted way that the survey was advertised, the risk of this seems small and well managed, especially given the time needed to re-complete the survey, using a different computer and email address.

To conclude, across multiple countries the impact of pain on analgesic dependence was mediated by frequency of analgesic use rather than overuse or abuse, and self-reported perceived need for analgesics was the strongest predictor of analgesic dependence. Asking people directly about feelings of needing analgesics could identify those who would benefit from interventions to reduce how often they use analgesics, which should reduce their risk of analgesic dependence.

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