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Risk to heroin users of poly-drug use of pregabalin or gabapentin

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ABSTRACT

AIM

To examine the risk to heroin users of also using gabapentin or pregabalin (gabapentoids).

DESIGN

Multidisciplinary study:- we (a) examined trends in drug related deaths and gabapentoid prescription data in England and Wales to test for evidence that any increase in deaths mentioning gabapentin or pregabalin is associated with trends in gabapentoid prescribing and is concomitant with opioid use; (b) interviewed people with a history of heroin use about their polydrug use involving gabapentin and pregabalin; (c) studied the respiratory depressant effects of pregabalin in the absence and presence of morphine in mice to determine whether concomitant exposure increased the degree of respiratory depression observed.

SETTING

England and Wales.

PARTICIPANTS

Interviews were conducted with 30 participants (19 males, 11 female).

MEASUREMENTS

(a) Office of National Statistics drug-related deaths from 1 January 2004 and 31 December 2015 that mention both an opioid and pregabalin or gabapentin; (b) subjective views on the availability, use, interactions, and effects of polydrug use involving pregabalin and gabapentin; (c) rate and depth of respiration.

RESULTS

Pregabalin and gabapentin prescriptions increased about 24% per year from 1 million in 2004 to 10.5 million in 2015. The number of deaths involving gabapentoids increased from less than one per year prior to 2009 to 137 in 2015; 79% of these deaths also involved opioids. The increase in deaths was highly correlated with the increase in prescribing (correlation

coefficient 0.965; 5% increase in deaths per 100,000 increase in prescriptions). Heroin users described pregabalin as easy to obtain. They suggested that the combination of heroin and pregabalin reinforced the effects of heroin but were concerned it induced 'black outs' and increased the risk of overdose. In mice, a low dose of S-pregabalin (20 mg/kg) that did not itself depress respiration reversed tolerance to morphine depression of respiration (resulting in 35% depression of respiration, $P < 0.05$) whereas a high dose of S-pregabalin (200 mg/kg) alone depressed respiration and this effect summated with that of morphine (producing over 50% depression of respiration, $P < 0.05$).

CONCLUSIONS

For heroin users the combination of opioids with gabapentin or pregabalin potentially increases the risk of acute overdose death through either reversal of tolerance or an additive effect of the drugs to depress respiration.

INTRODUCTION

The gabapentoids, gabapentin and pregabalin, are first-line treatments for various forms of neuropathic pain and are licensed for the treatment of some forms of epilepsy. They are also widely used off-label for other disorders including anxiety (pregabalin), insomnia, migraine, mania, bipolar disorder and alcohol withdrawal (gabapentin). These drugs were originally classified as having low abuse potential. However there have been reports of gabapentin and pregabalin being misused with subsequent development of dependence [1-4] and recent reports of gabapentin and pregabalin misuse in subjects with a history of opioid use [5-9]. Behavioural effects of these drugs related to their misuse include relaxation, enhanced sociability, euphoria and at higher doses dissociation and sedation.

Concerns about over prescribing of gabapentin and pregabalin led Public Health England and NHS England to issue prescribing advice for these drugs in 2014 [10]. Clinical guidelines on the management of neuropathic pain in both general and special settings (such as prisons) have emphasised caution in the use of gabapentoids because of their potential for misuse and diversion, however the specific issue of increased overdose death has not been emphasised in this context [11,12]. A study of toxicology reports of drug-related deaths in Finland in 2010-2011 [13] suggested there had been a substantial increase in drug related deaths involving pregabalin and opioids. In two opioid treatment programmes in Ireland and Germany 10% of patients tested positive for pregabalin by urine analysis; the majority without being prescribed the drug for any medical purpose [5,6].

We conducted a multi-disciplinary study to examine the risk of polydrug use involving opioids and pregabalin or gabapentin. We examined trends in the number of drug poisoning deaths in England and Wales to assess whether there has been an increase in the number of pregabalin or gabapentin fatal poisonings and whether the increase is associated with concomitant opioid use. People with a history of heroin use were interviewed about their use of pregabalin and gabapentin, and their perception of the dangers of co-use with opioids. We also determined in mice the respiratory depressant effects of pregabalin in the absence and presence of morphine to see if concomitant use increased the likelihood of overdose death from respiratory depression.

METHODS

Drug Related Poisoning Deaths

The Office for National Statistics (ONS) has developed a database of drug related deaths in England and Wales (based on International Classification of Disease codes) that identifies the specific substances involved [14,15]. The information is obtained from death certificates issued by coroners after investigation of the death, supported by forensic toxicology. ONS only has access to information specified on the death certificate and does not have access to the full toxicology report. Guidance on the limitations of the data held by ONS are given in reference 15. Data on the number of drug related deaths where pregabalin or gabapentin were mentioned, and whether or not the record also mentioned an opioid, were extracted for deaths registered between 1st January 2004 and 31st of December 2015. The number of community prescriptions per annum for pregabalin and gabapentin in England and Wales were obtained from the Health and Social Care Information Centre (HSCIC). We used correlation coefficient and linear regression to test whether there was a positive association between trends in gabapentoid prescription and drug related deaths mentioning pregabalin or gabapentin. Drug related deaths data had 1 added to each year record (because no deaths observed in 2005, 2007 and 2008) and were then log-transformed so that residuals from the linear regression model were normally distributed [16]. As a sensitivity analysis around the addition of 1 as a constant to the death data, we re-ran the regression model after dropping the year records with no deaths.

Interviews with heroin users

Bristol Drugs Project (BDP), the selected location for this study into polydrug abuse amongst heroin users, is located close to the city centre and offers a range of facilities for service users who are on varying drug treatments and at different stages of treatment. The study was

approved by the Faculty of Medical and Dentistry Committee for Research Ethics, University of Bristol. A purposive sample (based on gender, drug treatment and duration of heroin use) were given information about the study and asked if they would be willing to take part in an interview.

A purposive sample (based on gender and duration of heroin use) were given information about the study and asked if they would be willing to take part in an interview. The staff of BDP had good background knowledge of how long people had been using heroin and assisted in identifying eligible participants. No-one who was approached actively rejected participating in the study, although three individuals who had verbally agreed to take part did not attend for interview at their allocated time. No-one withdrew from the study once written consent was given.

Interviews were conducted with 30 participants. The sample size was partly pragmatic in terms of the study timetable, but was designed to include a range of heroin users. Data saturation was reached in that no new issues were emerging towards the end of the interview process. The final sample comprised 19 males and 11 females of whom: 20 were long-term drug users who had used heroin for over 10 years; four had used heroin between 5-10 years, and; six were shorter-term drug users who had used heroin for under five years. Each participant was interviewed once by AL between October 2014 and February 2015, and was given £10 to compensate them for their time. Interviews were conducted in a private consultation room and digitally recorded with the written consent of the participant. Interviews lasted between eight and 52 minutes, with the mean length of interview being 25 minutes (excluding the initial introduction and consent procedures). All interviews were conducted by the same researcher (AL) using a topic guide designed to identify patterns and

types of polydrug use, and participants' perceptions of any benefits and disadvantages to polydrug use.

Recordings were transcribed verbatim, anonymised and transferred into Nvivo10 software (QSRinternational, UK) to aid analysis. Thematic analysis was undertaken using Framework and Nvivo software [17]. Sections of text were coded by AL according to specific drugs used, and participants' perceptions of their interactions and effects. SA checked coding and interpretation, with any discrepancies resolved through discussion between AL and SA. Data presented here relate to the key themes identified in relation to polydrug use involving gabapentoids.

Respiration studies

Male CD-1 mice (Harlan Laboratories, UK) weighing approximately 30g were maintained at 22°C on a reversed 12 hour dark:light cycle with food and water available *ad libitum*. All experiments were performed in the dark (active) phase. Animals were randomly ascribed to treatment groups (N = 6 or 7) with the experimenter blinded to the drug treatment. Respiration was measured in freely moving animals using plethysmography chambers (EMKA Technologies, France) supplied with a 5% CO₂ in air mixture (BOC Gas Supplies, UK) as described previously [18]. Rate and depth of respiration were recorded and converted to minute volume (MV). Only animals whose initial pre-drug MV was between 120 and 185 ml/min were included in this study. Data were analysed using an unpaired Student's t-test and a statistically significant difference assumed when P<0.05. All procedures were performed in accordance with the UK Animals (Scientific Procedures) Act 1986, the European

Communities Council Directive 1986 (86/609/EEC) and the University of Bristol ethical review document.

Drugs used were morphine hydrochloride (Macfarlan Smith, UK), naloxone hydrochloride (Sigma Aldrich, UK), S/R-pregabalin and S-pregabalin (synthesized and purified at the University of Bristol). S/R-pregabalin was used in our initial experiments but we switched to S-pregabalin (the active isomer) when sufficient stocks became available. To induce tolerance to morphine mice were either implanted subcutaneously with a morphine pellet (75mg morphine base, National Institute on Drug Abuse, USA) or an osmotic minipump (Alzet) that released morphine 45mg/kg/day for six days [18].

RESULTS

Deaths involving pregabalin and gabapentin

Figure 1A shows trends in the number of prescriptions for gabapentoids (pregabalin and gabapentin) in 100,000s with the number of drug related deaths mentioning gabapentoids in total and those mentioning gabapentoids and opioids. There has been an annual 24% increase in the number of gabapentoid prescriptions in England and Wales from approximately 1 million in 2004 to over 10 million in 2015. Deaths in which pregabalin or gabapentin was mentioned on the death certificate increased from less than 1 per year before 2009 to 137 deaths in 2015. In 79% of these deaths (216/275) opioids (heroin, methadone, other or non-specific) were also mentioned. The increase in deaths was highly correlated with prescribing data (correlation coefficient 0.94; Figure 1B). For each 100,000 increase in gabapentoid prescription, the number of deaths increased by approximately 5% (risk ratio (RR) 1.05 95%CI 1.03-1.06 $p < 0.001$) which is equivalent to a RR of 1.64 for an increase of 1 million prescriptions and an RR of 88.4 for an increase of 8 million prescriptions. After transforming

the deaths data there was no evidence of non-normality (Shapiro-Wilk W test for normal data $p = 0.75$; Cameron & Trivedi's test against heteroskedasticity $p=0.11$. Excluding years without any deaths did not alter the findings (correlation coefficient 0.965; RR 1.047).

Heroin users' perceptions of combining heroin and pregabalin or gabapentin

All interview participants were, or had been, active heroin users and some were on an opioid substitution treatment. Participants reported ease of access to gabapentoids. Of the 30 participants interviewed, 21 had experience of pregabalin or gabapentin. Two participants used gabapentin, stating they used it daily and sourced it from friends who were prescribed it. Of the 19 pregabalin users: one was a daily user; three used it weekly; five used it rarely, and 10 stated it was just a one-off occasion. Pregabalin was taken orally in tablet form, and doses ranged from 300mg to 1500mg. Some participants said they were prescribed pregabalin by a doctor, usually as they had some kind of nerve damage from previous accidents, but others suggested pregabalin could be purchased on the street for approximately £2 per 300mg tablet.

Pregabalin enhances the effect of heroin

Participants highlighted growing recognition that the combination of heroin and pregabalin could enhance the effect of the heroin. Ian, aged 51, a long-term heroin user who took pregabalin on a daily basis, indicated: *"I'm prescribed it for a reason, for nerve damage but I didn't know what was going on until later on, later on like in my using, that it was enhancing, enhancing the feeling of the heroin whereas I thought it was just better heroin [laughs] at the time. So I was naive to the fact of that but now I'm well, well, well versed in like knowing what that is all about."* Similarly Edward, aged 34 and a short-term heroin user who took pregabalin rarely, suggested: *"If anything the heroin's helped the pregabalin work quicker and maybe stronger ... so they both sort of work same sort of way."*

Pregabalin might reduce heroin use

Because of the belief that the drugs had similar effect, it was asserted that pregabalin might decrease heroin use for some people. James, aged 58 and a long-term heroin user, said he had used pregabalin three times and added: *You don't really want to use heroin, you want more pregabs, I don't know why.*” Kate, aged 35, a long-term heroin user who said she had rarely taken pregabalin, suggested it might assist with heroin withdrawal: *“Last time I used I took two, two of 250 pregabalins and I went home. And I've got two of each [heroin and crack cocaine] in my pocket for instance, yeah. Put it down on the coffee table and normally I would be desperate – open it up, you know, doing it. I just, I was just so like chilled out watching TV and the next thing I know I woke up the next morning and the two things, four things [heroin and crack cocaine] were still on the table and I felt really good about myself, I hadn't used because, for some reason. And loads of other addicts have said the same to me as well. It [pregabalin] would be a brilliant drug to bring out in a detox unit, just to be used for like one or two days, just when you're feeling the shittiest, because it really, it really does, it just chills you out.”*

Pregabalin causes blackouts/loss of control

The combination of heroin and pregabalin was thought to be the cause of blackouts and loss of control. Cleo, aged 23 and a short-term heroin user, said she had rarely used pregabalin: *“The effect on me it's like I had blackouts because the next day I wakes up and I can't remember nothing what happened.”* Edward, aged 34 and a short-term heroin user, also said he rarely used pregabalin: *“Most people that I know who's took pregabalin around me, cos I've not took many myself but I've known people who takes them to get wrecked, is um they're like zombies, they don't know what they're doing.”*

Concerns were raised that these blackouts could have serious implications for the user. Jacob, aged 44 and long-term heroin user who used pregabalin on a weekly basis, suggested: *“By the time it hits the pregabs you’re already out of your head so, you know what I mean, you could end up doing a hit that you wouldn’t usually do because you’re not really with it.”*

Pregabalin and overdose

Of the participants who took pregabalin, most believed it increased the risk of overdose. Ian, aged 51 and long-term heroin user, used pregabalin daily: *“That’s one of my last overdoses. I knew the heroin was strong and I didn’t know, I was naive to the fact, that pregabalin is an enhancer as well as what it’s used for medically like on my body.”* Helen, aged 36 and another long-term heroin user who took pregabalin every day, suggested pregabalin had a delayed effect which could increase the risk of overdose for an impatient user: *“Pregabalin takes like two, three hours to kick in so, like, and then we think “Argh it hasn’t kicked in, I’ll have a dig”. So we have a dig and then that kicks in and then there’s more chance of you going over ... overdosing, that’s the danger.”*

Effect of pregabalin on respiration

Pregabalin depression of respiration

The heroin users we interviewed indicated a preference for pregabalin and therefore we examined the effects of pregabalin rather than gabapentin on respiration in mice. In the early stages of the study we only had S/R-pregabalin available to us. We observed that S/R-pregabalin (40–400 mg/kg i.p.) produced dose-dependent depression of respiration. When S-pregabalin, the active pregabalin isomer in Lyrica [19], became available we demonstrated that a 200mg/kg dose of this isomer produced similar respiratory depression to 400 mg/kg of

the racemate (compare the depression of respiration by pregabalin in Figures 2B and 3B). S-pregabalin produced profound depression of respiration that developed rapidly, within five minutes of drug injection, and was maintained for the remainder (30 minutes) of the observation period (Figure 2A & B). When respiration was depressed by pregabalin it became regular, there was no evidence of apnoea or gasping, and resulted from a decrease in both rate and depth of respiration (Figure 2C). Pregabalin did not induce ribcage muscle stiffness which would reduce tidal volume. The depression of respiration by 200mg/kg S-pregabalin was similar to that induced by 10mg/kg morphine (Figure 2B). The depression of respiration by pregabalin was not however due to release in the brain of endogenous opioids or to direct activation of opioid receptors as, unlike the depression which occurs to morphine, it was not prevented by prior administration of naloxone (Figure 3A).

When administered to the same animal the respiratory depressant effects of S/R-pregabalin and morphine appeared to summate rather than show synergism (Figure 3B). The depression of respiration by morphine after S/R-pregabalin was similar in extent to that seen in animals not pretreated with S/R-pregabalin (Figure 3C). In mice that had been rendered tolerant to morphine by continuous exposure to the drug over six days, S/R-pregabalin produced the same degree of respiratory depression as seen in morphine-naïve mice (Figure 3D).

Pregabalin reversal of morphine tolerance

Following six days treatment with morphine an acute challenge with morphine (10mg/kg) failed to depress respiration demonstrating that the mice were tolerant (compare Figure 2B and Figure 4B). To investigate the effect of pregabalin on morphine tolerance we gave mice that had been treated with morphine for six days an acute injection of S-pregabalin (20mg/kg i.p.) at the same time as the challenge dose of morphine. This dose of S-pregabalin alone

produced very little depression of respiration in both naïve mice and mice pretreated with morphine (Figure 4A). In morphine-pretreated mice that were injected with S-pregabalin at the same time as the acute morphine challenge respiration was significantly depressed (Figure 4B). This is consistent with pregabalin reversal of morphine tolerance.

DISCUSSION

Main Findings

Concomitant use of heroin and gabapentoids (pregabalin and gabapentin) is an emerging public health problem. Fatal poisonings, the majority involving opioids, have increased substantially and are strongly correlated with the increase in prescriptions. Heroin users reported ease of access and increasing use of gabapentoids which, if taken with heroin, can induce blackouts and may increase overdose risk. In laboratory animal experiments a low dose of pregabalin was observed to reverse morphine tolerance and reveal respiratory depression to a dose of morphine that did not depress respiration in tolerant animals; whereas a high dose of pregabalin itself depressed respiration in opioid naïve animals and this was additive with morphine. Taken together our data corroborate the hypothesis of an increase in overdose risk when gabapentoids are used along with opioids.

Strengths and limitations

We are unaware of any other studies that combine epidemiological, qualitative and pharmacological laboratory experimental insights on overdose risk, and believe our study demonstrates the benefits of combining different research methods in the study of risk. However, there are limitations that need to be taken into account. Information on drug related poisonings is based on drugs specified by the coroner on the death certificate. About 10% of poisoning deaths have no specific information, and not every drug detected in forensic tests

will be reported on the death certificate [20]. Approximately one in three fatal poisonings mention more than one substance and 30% mention alcohol and it is not always clear which substance or substances is responsible for the fatality [15]. We are not aware, however, of any alteration in practice by coroners that would increase the likelihood of reporting pregabalin or gabapentin on death certificates. We show a strong ecological association between trends in gabapentoid prescriptions and overdose deaths but from the data available to ONS we are unable to say how many acute poisoning deaths in which both opioids and gabapentoids were reported are illicit opioid users or how many are patients prescribed both opioids and gabapentoids for pain. The majority of people dying from opioid poisoning, however, are problem drug users. Moreover, given the ready availability of gabapentoids to illicit opioid users (as reported in our interviews with heroin users) and the perceived higher incidence of overdose (non-fatal and fatal) amongst illicit opioid users it is likely that they are the larger cohort.

Our interviews with heroin users were by necessity undertaken on a relatively small sample of participants and cannot be generalized to a wider population. However, we were able to interview a range of heroin users of both genders whose accounts are authentic and give insight into the views and experiences of polydrug use involving heroin and gabapentoids. Finally, in the study of the effect of pregabalin on respiration we did not attempt to determine the mechanism by which the observed depression occurred save that it was produced by S-pregabalin, the active isomer of pregabalin used clinically in the treatment of pain, and that it did not involve either the release of endogenous opioids or direct activation of opioid receptors.

How our evidence fits with other studies

An association between the presence at post mortem of opioids and gabapentoids has previously been observed in a Finnish study of drug-related deaths [13]. They observed that opioids were present in around 90% of the deaths where there was evidence of pregabalin or gabapentin misuse. They also reported that the incidence of pregabalin misuse in drug related deaths was over 7-fold greater than that of gabapentin. This may be because pregabalin is more rapidly absorbed and has higher bioavailability than gabapentin following oral administration [21].

Potentially the presence of pregabalin or gabapentin in opioid overdose fatalities could have been benign and not a factor in overdose, their presence simply being due to recent misuse of these drugs by heroin users. However, there is evidence now from multiple sources that gabapentoids potentiate the effects of opioids. A survey of opioid users suggested pregabalin and gabapentin potentiated the high obtained with methadone [22]. Also, the heroin users we interviewed reported that gabapentoids enhanced both the high and the likelihood of overdose.

In animal experiments pregabalin has been reported to enhance the sedation induced by oxycodone and morphine [23] while gabapentin can inhibit both the development and maintenance of tolerance to the antinociceptive effects of morphine [24]. We observed that morphine and pregabalin were additive in depressing respiration and a low dose of pregabalin could reverse tolerance to the respiratory depressant effects of morphine. Both of these effects would result in enhanced respiratory depression and further supports the view that gabapentoids can contribute to heroin fatalities.

Implications

Heroin users are notorious polydrug users frequently using alcohol, benzodiazepines and crack cocaine as well as heroin [25]. To this list we can now add the gabapentoids which are now widely prescribed for a range of disorders. The substantial rise in prescriptions illustrated in Figure 1 seems unlikely to be due simply to an increase in cases of neuropathic pain [26]. Their uncontrolled status may lead to over-prescribing particularly to those with a history of substance/opioid misuse [4]. Also, the absence of objective parameters for the severity of the conditions for which pregabalin and gabapentin are prescribed may make it easy to obtain high doses of these drugs, simply by reporting poor effectiveness, or by reporting symptoms that do not exist [8]. This may also facilitate diversion. Though guidelines for pain management recommend caution in the use of gabapentoids because of the risk of misuse and diversion, these issues are not highlighted in current guidance on the management of opioid dependence. Similarly, the specific problem of increased overdose risk associated with gabapentoids is not emphasised in current overdose prevention guidelines for problem opioid users. In contrast the increase in methadone prescription after the introduction of supervised consumption was not associated with an increase in methadone related overdose deaths [27]. In the broader context these issues reflect the challenge of the management of chronic non-cancer pain in the community. Pain is a symptom and is not amenable to objective measurement. Chronic pain, including “neuropathic” pain, is extremely common and is mainly managed by clinical generalists working in Primary Care [28]. Faced with an apparently distressed and demanding patient who reports that their pain has not been controlled by other treatments, GPs may feel pressure to prescribe an alternative, particularly when there is some evidence that this alternative is effective [29].

Gabapentin or pregabalin are currently being prescribed to heroin users, or can be purchased on the street. It is important that doctors and their patients are aware that the combination of opioids with gabapentin or pregabalin potentially increases the risk of acute overdose death through either reversing tolerance or by an additive effect of the drugs to depress respiration. Alternatives to gabapentoids need to be recommended for clinicians managing opioid dependent patients with neuropathic pain or generalised anxiety, and greater attention given to restricting diversion of gabapentoid prescriptions.

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FIGURE LEGENDS

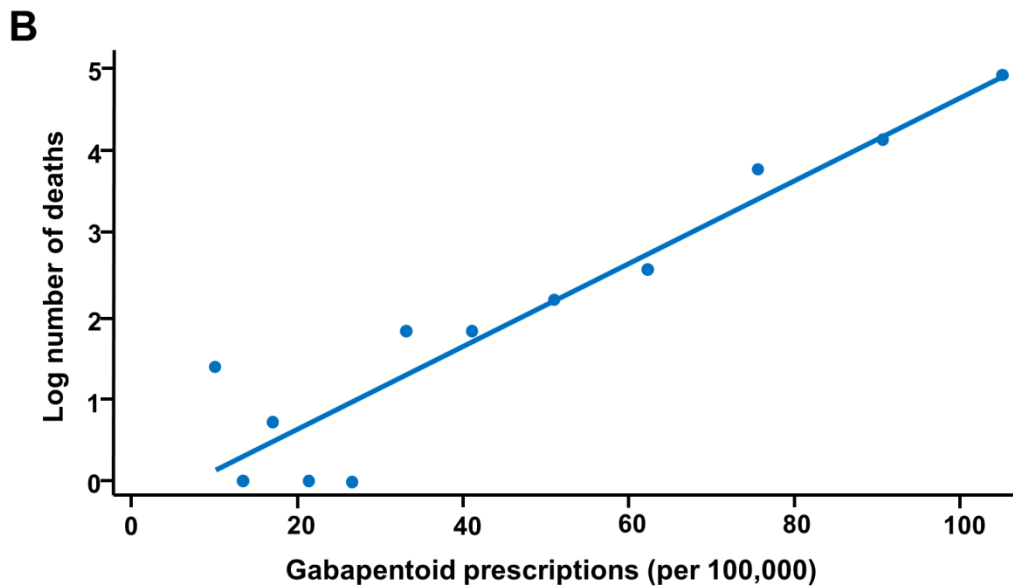
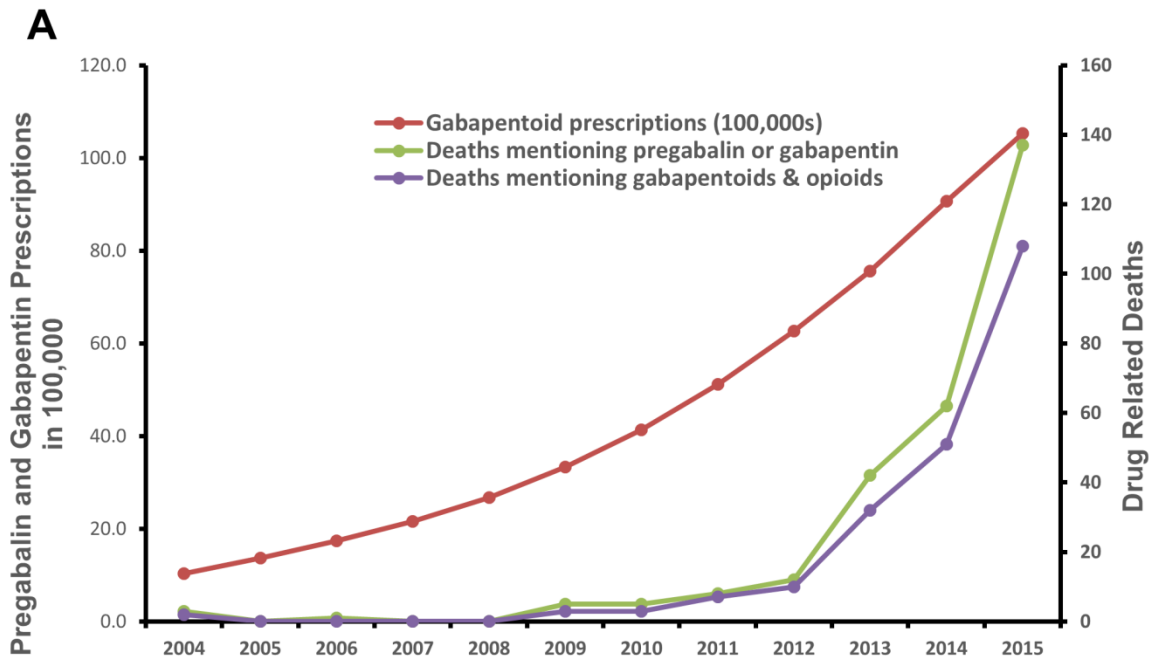


Figure 1. Number of pregabalin and gabapentin prescriptions and number of deaths per annum in which pregabalin and gabapentin were mentioned on the death certificate from 2004 - 2015.

A. The number of community care prescriptions per annum for pregabalin and gabapentin in the England and Wales are shown in red. Data were obtained from the Health and Social Care Information Centre (HSCIC, UK). The number of registered deaths per annum in England and Wales in which pregabalin or gabapentin were mentioned on the death certificate is shown in green. The number of deaths in which pregabalin and gabapentin as well as an opioid drug were mentioned are shown in purple. Data obtained from the Office for National Statistics (ONS, UK). **B.** Scatter plot of gabapentoid prescriptions (per 100,000) in England and Wales (2004 to 2015) versus overdose deaths (on a logarithmic scale) in which gabapentoids were mentioned in the coroner's report. Data are replotted from that used in A. The blue line shows line of best fit (correlation coefficient 0.965): 5% increase in overdose deaths per 100,000 increase in prescriptions.

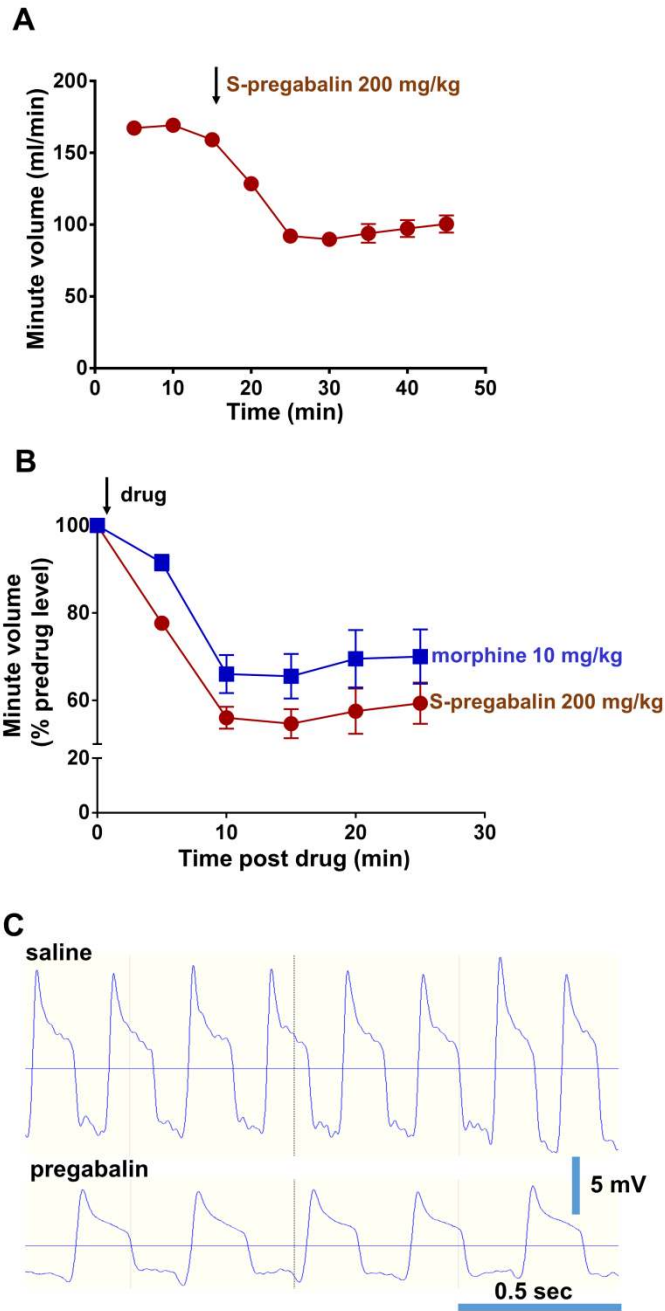


Figure 2. Depression of respiration by pregabalin and morphine in the mouse. A. Inhibition of respiration by S-pregabalin (200 mg/kg ip). Data are shown as minute volume before and following drug injection. N = 6. In some instances error bars are smaller than the symbol. **B.** Comparison of inhibition of respiration by S-pregabalin (200 mg/kg ip) and morphine (10mg/kg ip). For each drug treatment then for each animal data are normalised to minute volume before drug injection. Data for S-pregabalin were derived from that

illustrated in part A. N = 6 for both drug treatments. C. Raw respiration traces from an untreated mouse and one injected with S/R-pregabalin (400 mg/kg ip) recorded at the height of drug action. The horizontal blue line indicates the point of pressure inflection. In the respiration traces expiration is upwards.

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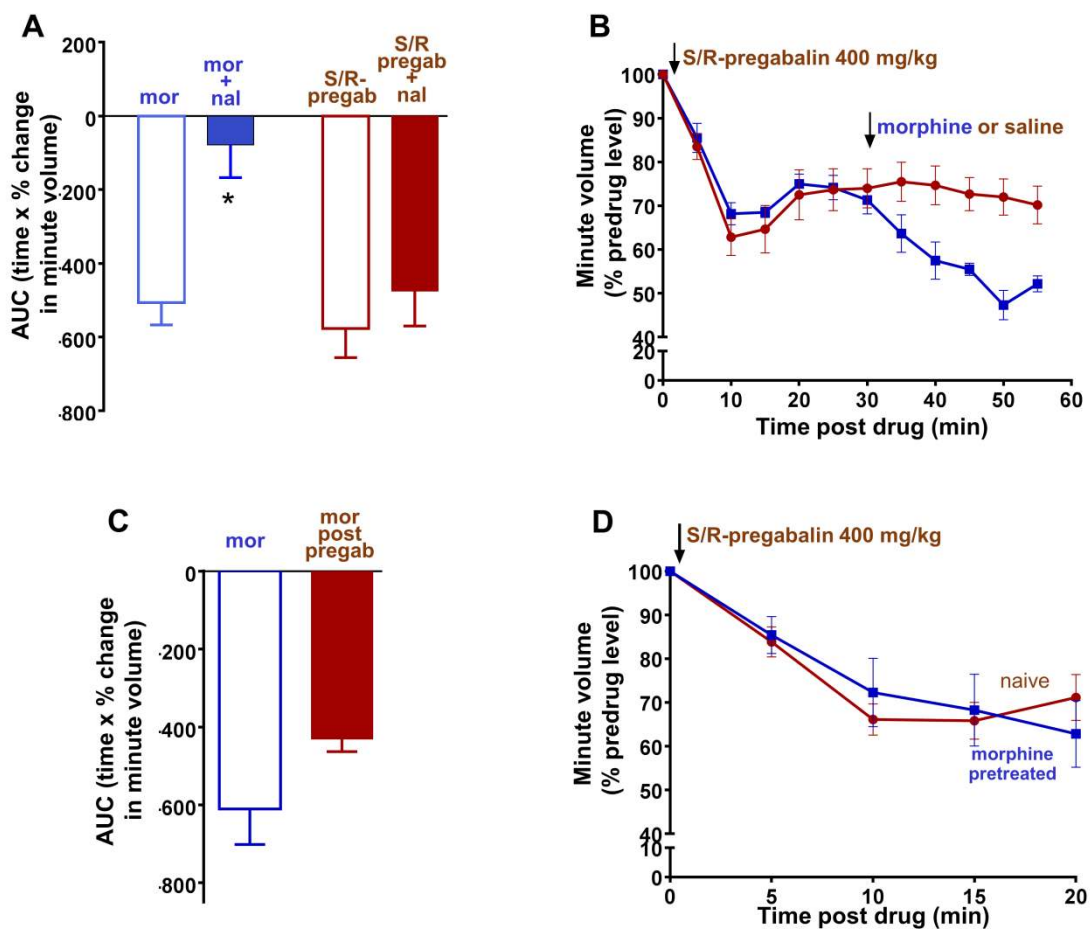


Figure 3. Interactions between S/R-pregabalin and morphine on mouse respiration. A. Pretreatment with naloxone (1 mg/kg ip; nal) for 10 min abolished the depression of respiration induced by morphine (10 mg/kg ip; mor) but not that induced by S/R-pregabalin (400 mg/kg ip, pregab). The area under the curve (AUC) for the percentage change in minute volume induced by each drug treatment has been calculated [see ref 18] and then the mean value determined. N = 6 in each case; * indicates $P < 0.05$, unpaired, two tailed Student's t test comparing morphine and morphine + naloxone. There was no statistical difference between pregabalin and pregabalin + naloxone. **B.** Depression of respiration induced by morphine (10 mg/kg ip, filled squares) or saline (filled circles) in mice that had been pretreated with S/R-pregabalin (400 mg/kg ip). **C.** Comparison of the depression of respiration induced by morphine in naïve animals and in animals pretreated with S/R

pregabalin (400 mg/kg). N = 6 in each case, there was no statistical difference (unpaired, two tailed Student's t test) between the treatments. **D.** Depression of respiration induced by S/R-pregabalin (400 mg/kg ip) in naïve mice and in mice that had been pretreated with morphine for 6 days. N = 7 in each case. Statistical analysis (unpaired, two tailed Student's t test) of the AUC for both treatments demonstrated that there was no statistical difference between the degree of respiratory depression induced by pregabalin in the naïve and morphine-treated mice.

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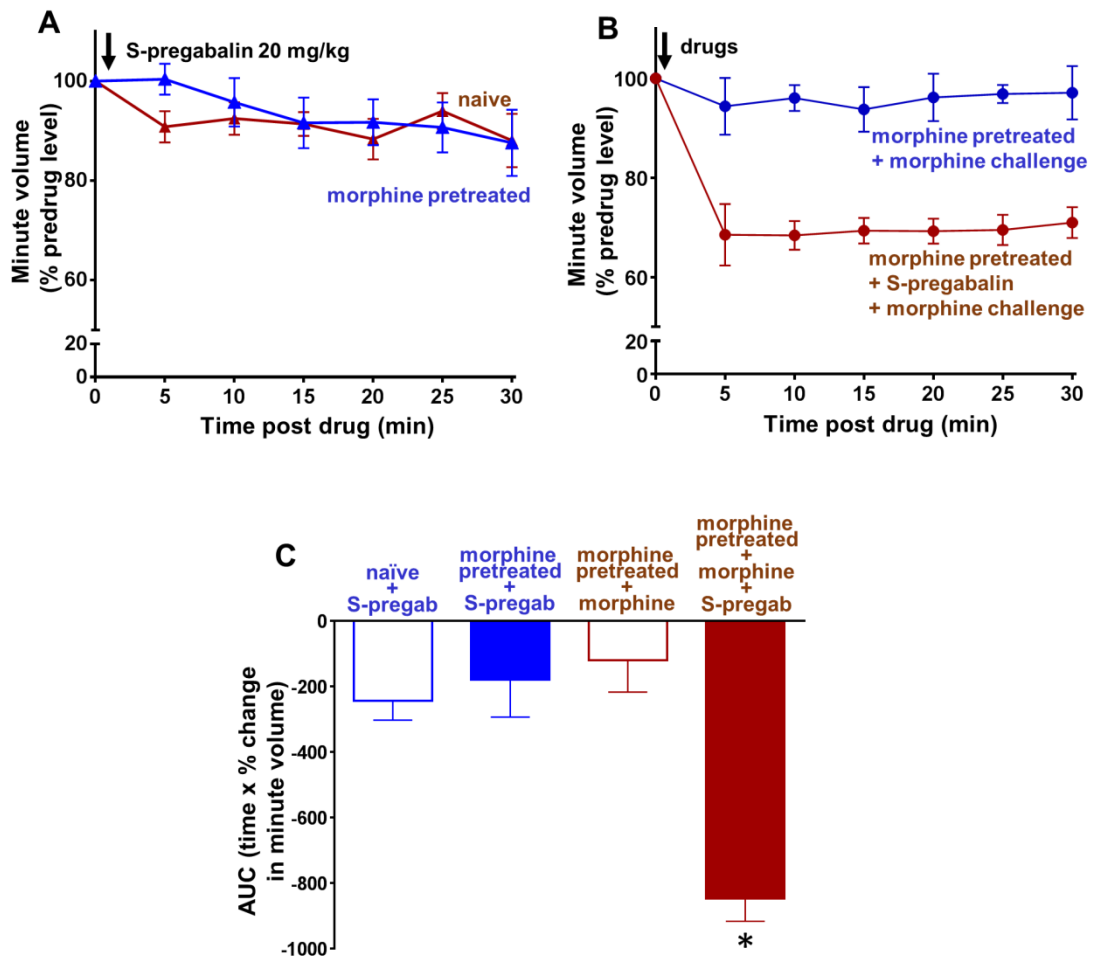


Figure 4. Reversal of morphine tolerance by S-pregabalin. **A.** The low dose of S-pregabalin (20 mg/kg ip) in naïve mice and mice that had been pretreated with morphine for 6 days produced little depression of respiration. N = 6. **B.** In mice that had been pretreated with morphine for 6 days acute injection of morphine (10 mg/kg ip) did not depress respiration i.e. the mice were tolerant. Whereas, with a simultaneous injection of pregabalin (20 mg/kg ip) injection of morphine (10 mg/kg ip) did depress respiration in mice that had been pretreated with morphine for 6 days. **C.** AUC analysis of the data in **A** & **B** [see ref 18] indicated that in morphine pretreated mice pregabalin + morphine induced significantly greater depression of respiration than morphine alone ($P < 0.05$). N = 6 in each case.