PREVENTION NOT CURE: AVOIDING A EUROPEAN PRESCRIPTION OPIOID EPIDEMIC

The opioid addiction crisis in the US and Canada is a pressing and immediate problem in today's healthcare landscape. Here, Damon Smith, PhD, Chief Executive Officer of Altus Formulation; Richard Dart, PhD, MD, Executive Director of RADARS System; and Christopher Hirst, Head of RPH Pharmaceuticals, Recipharm, discuss the causes and possible solutions to the epidemic, as well as whether or not Europe is likely to face a similar fate.

PRESCRIPTION OPIOID ABUSE

In the US, the number of people dying from prescription opioid overdose is shocking. The US Centers for Disease Control and Prevention estimates that, from 1999 to 2016, over two hundred thousand deaths have occurred this way,[1] in 2016, 46 people died every day.

> "Canada runs a very different healthcare system to the US, yet Health Canada reports that in 2016 there were almost 3000 opioid related deaths,[3] which translates to about eight people dying per day."

Some may argue America is a special case and that a prescription opioid epidemic could never happen in Europe. They argue that, in the US, pharmaceutical companies underplayed the addictive properties of opioids and physicians over-prescribed them. In part they may be correct, however such practices are not unique to the US.[2]

Such marketing tactics also fail to account for Canada's prescription opioid problem. Canada runs a very different healthcare system to the US, yet Health Canada reports that in 2016 there were almost 3000 opioid related deaths,[3] which translates to about eight people dying per day. As the Canadian population is 10 times smaller than the US, these figures are alarming. Arguments that Europe is immune to an opioid crisis because of its different prescribing habits must be viewed very critically.

Putting the Genie Back

Both Canada and the US are now implementing multi-focal approaches to address their prescription drug abuse problems. Whilst they are starting from a disadvantaged position, addiction having already taken hold in their populations, evidence supports the new controls are taking effect.[4]

In general, the approach being taken in North America is four-pronged:

1. Better physician training and controls on prescribing
2. Increased efforts and treatment options for addict rehabilitation
3. The introduction of abuse deterrent opioid/stimulant formulations, including incentives for generic approaches
4. Increased surveillance to track rates of abuse and monitor for signs of effectiveness.

As Figure 1 shows, Europeans are consuming ever increasing amounts of opioids. Europe has the opportunity to learn from the North American experience and, in doing so, avoid its own opioid epidemic. Without due attention this possibility is a real one, as this article will discuss.

THE NEED FOR EFFECTIVE PAIN CONTROL

In order to address prescription opioid abuse it's essential to understand why such drugs are necessary; attempts to prevent abuse cannot limit access to patients.

Chronic Pain

It is a cliché to point out that we live in an ageing world, but it is evidently true. From 1990 to 2014, the life expectancy for an adult

Dr Damon C Smith
Chief Executive Officer
T: +1 514 883 3447
E: dsmith@altusformulation.com

Altus Formulation Inc
17800 Rue Lapointe
Mirabel Quebec
J7J 1P3
Canada

www.altusformulation.com

Dr Richard Dart
Executive Director, RADARS System
T: +1 303 389 1240
E: rdart@rmpdc.org

Rocky Mountain Poison and Drug Center
Denver Health and Hospital Authority
777 Bannock Street, Mailcode 0180
Denver, CO 80204
United States

www.rmpdc.org

Christopher Hirst
Head of RPH Pharmaceuticals
T: +44 161 342 6011
E: chris.hirst@recipharm.com

Recipharm AB
Box 603
SE-101 32 Stockholm
Sweden

www.recipharm.com

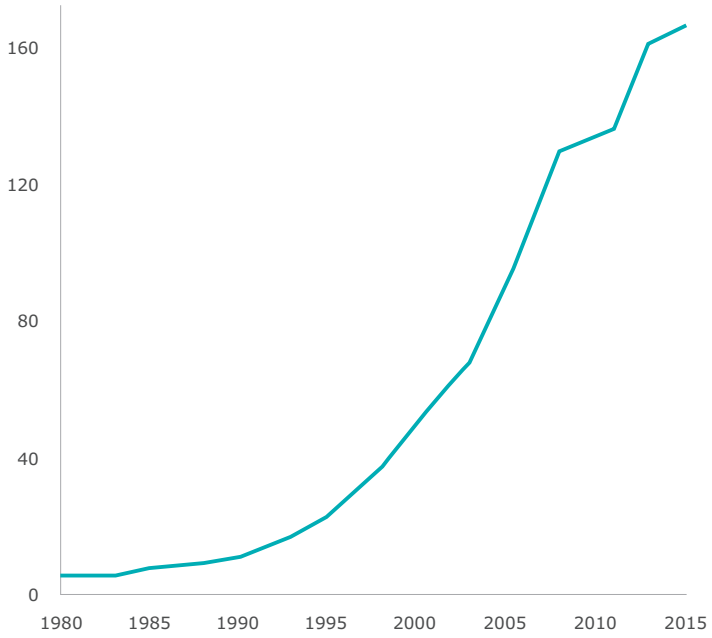

Figure 1: European Total Opioid Consumption 1990-2015 (mg/capita).

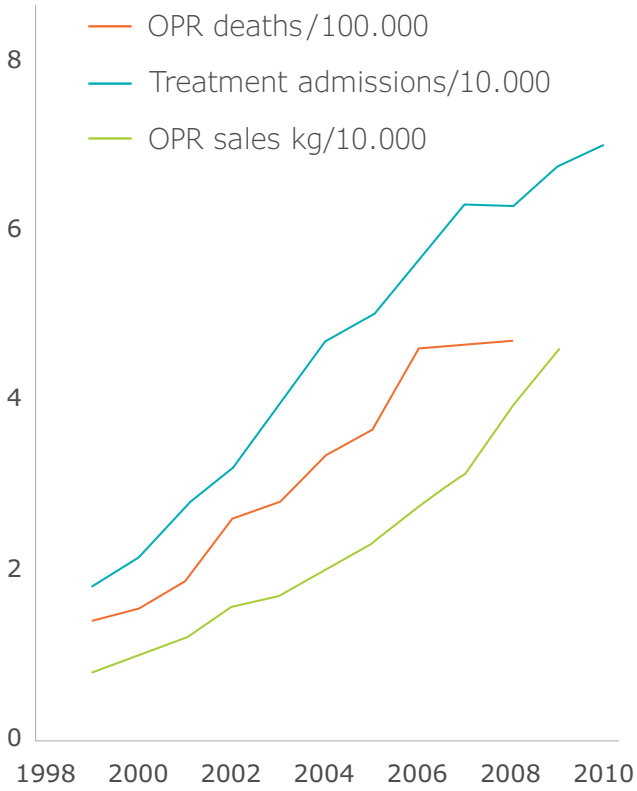

Figure 2: Rates of opioid pain reliever (OPR) overdose death, treatment admissions, and kilograms of OPR sold, 1999–2010.

"When chewing no longer satisfies an addiction, tablets may then be crushed and snorted (insufflation) or crushed and mixed with liquids and injected, a case in which overdose is common."

in the EU grew by some six years.[5] It is also a cliché that with greater age comes greater pain, but sadly this also is true; approximately 20% of European adults suffer from chronic pain and the prevalence is greater in older people.[6] If not well treated, chronic pain sufferers are more likely to be depressed, take more time off work and, despite the general upward trend, have a lower life expectancy,[7] all of which poses a significant societal cost. Effective remedies like prescription opioids are needed to address the growing incidence of chronic pain.

Acute Post-Operative Pain

Similar growth is seen in the number of patients requiring post-operative pain relief. For example, in the UK, approximately four million surgeries are performed every 12 months, equating to a European total of 45 million operations per year. This number is growing 5.5% annually and 80% of patients experience post-surgery pain requiring analgesia. Opioid narcotics are the most widely prescribed analgesics in this setting today as they offer fast and effective treatment in both inpatient and outpatient settings.[8]

Cancer Pain and Palliative Care

Cancer is typically a later life disease and patients suffering cancer pain, as well as those requiring effective palliative care, frequently rely on oral opioids. In these circumstances, eventually there are no alternative medications.[9]

To conclude, the 10% increase in prescribing of pain medications by German physicians in the last few years is typical of the EU as a whole[9–12] and reflects the needs our ageing population and changing lifestyles have for effective analgesia.[13] In many cases there are no alternatives to opioid analgesics, which will be needed in increasing amounts.[14]

Opioid consumption in Europe today (Figure 1) is rising at rates seen in North America in the early years of this century. The growing number of calls to redress these increases are well founded, as the link between opioid sales and deaths from prescription opioid abuse has been conclusively established (Figure 2).[15–18]

ABUSE DETERRENT FORMULATIONS

The Road to Addiction

The path from abuse of prescription drugs to addiction and death has been described many times. Figure 3 summarises this principle, beginning with susceptible patients swallowing multiple tablets to achieve euphoria. As tolerance and dependence take hold, such behaviours may progress to more dangerous forms of abuse where tablets are chewed before swallowing to release drug more rapidly, an approach to which extended release tablets containing large amounts of drug have been particularly vulnerable. When chewing no longer satisfies an addiction, tablets may then be crushed and snorted (insufflation) or crushed and mixed with liquids and injected, a case in which overdose is common.

"Abuse deterrent formulations, while not eliminating overdose risk, make it harder for overdose to occur."

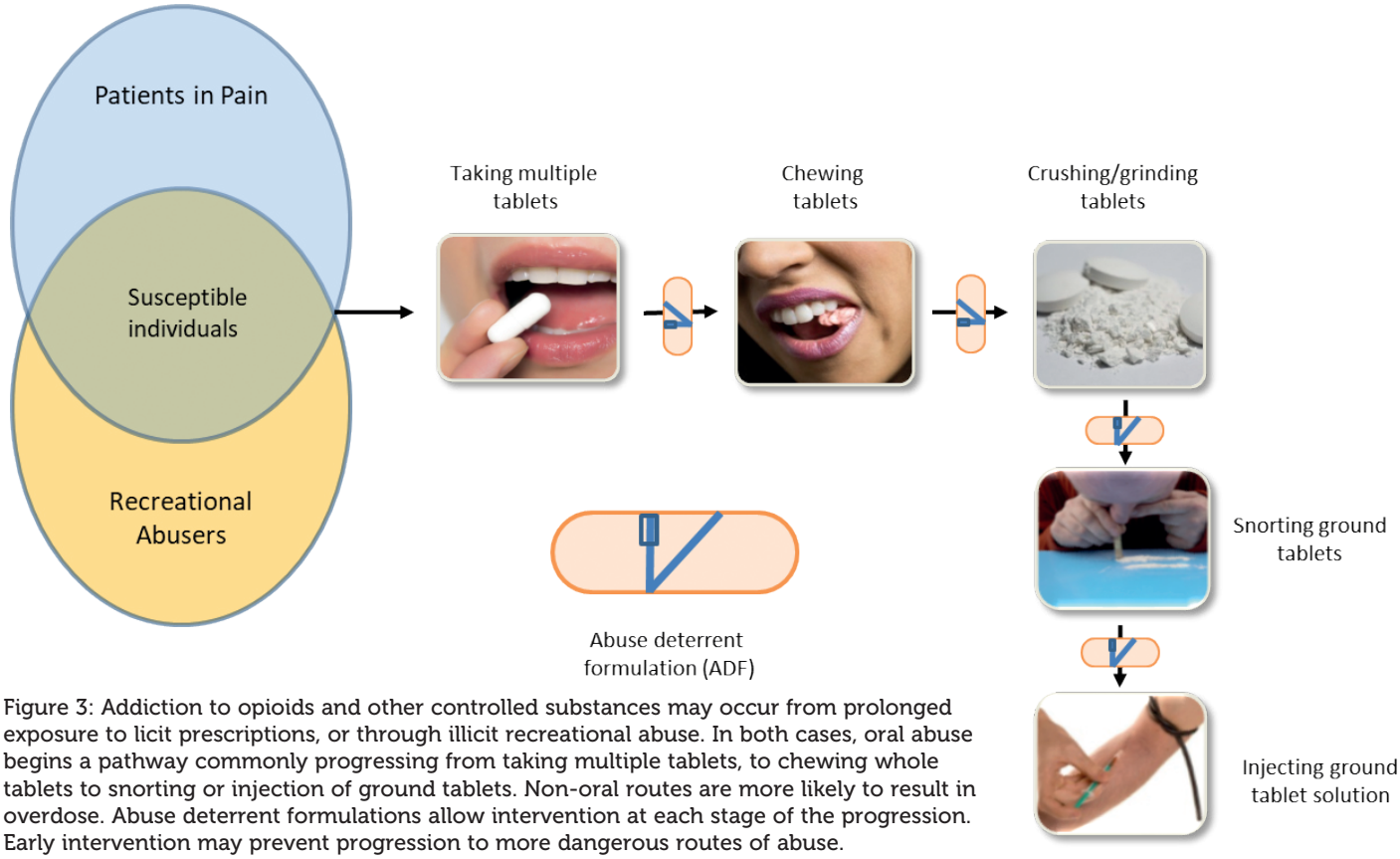

Figure 3: Addiction to opioids and other controlled substances may occur from prolonged exposure to licit prescriptions, or through illicit recreational abuse. In both cases, oral abuse begins a pathway commonly progressing from taking multiple tablets, to chewing whole tablets to snorting or injection of ground tablets. Non-oral routes are more likely to result in overdose. Abuse deterrent formulations allow intervention at each stage of the progression. Early intervention may prevent progression to more dangerous routes of abuse.

Prevention not Cure

Intervening in this progression by reducing the potential for chewing, insufflation and injection provides an opportunity to reduce overdosing and deaths.[19] Such intervention would be especially valuable in the early stages of abuse, i.e. as a preventative measure to avoid addiction rather than as a cure for the addict. Abuse deterrent formulations (ADFs), while not eliminating overdose risk, make it harder for overdose to occur. In principle they employ two basic approaches:

1. **Physicochemical Barrier Technologies** – Here, tablets are hardened to make them difficult to chew and resistant to crushing and grinding. Realising that no technology is immune to such attempts, technologies may also include excipients that swell in the presence of liquids to form a viscous gel that reduces the potential for injection.

   Examples of such technologies include heat-treatment recrystalisation (HTR), used on reformulated OxyContin® (Purdue Pharma, Stamford, CT, US), DETERx®, employed by Collegium Pharma (Canton, MA, US), and INTELLITAB™, developed by Altus Formulation (Figure 4).

2. **Agonist/Antagonist Technologies** – In this case, formulations comprise a separate antagonist included to counteract the effect of the opioid narcotic should the tablets be tampered with prior to ingestion. Whilst these products do not prevent the abuse *per se*, they are nevertheless designed to prevent harmful outcomes should abuse occur.

   Examples of products using this approach include Embeda®, a morphine sulphate/naltrexone formulation marketed by Pfizer, and Targiniq®, an oxycodone/naloxone formulation developed (but never marketed) by Purdue Pharma.

Seat Belts for Tablets

ADFs can be thought of as similar to seat belts, i.e. a simple to use, effective technology that makes any vehicle safer to use. This is due to three factors:

1. **Effectiveness** – Experience has proven seat belts to be effective and the same can be said of ADFs. For example, Severtson *et al*[20] and Dart *et al*[21] report, amongst other positive trends, that introduction of HTR barrier technology resulted in a reduction of 75% in the number of intentional abuse cases presenting to poison control centres and a reduction of 87% in the amount of non-oral abuse of the product.

Figure 4: The hard, coloured gel that forms immediately when Intellitab™ tablets are ground and added to liquids.

"Opioid narcotics, while a critically important case, are not the only drug that could benefit from an ADF approach, for example the popular press has recently highlighted abuse of gabapentinoids and benzodiazapines."

2. **Simplicity** – All abuse deterrent formulations are simple to use since, in appearance and administration, they are identical to any other tablet. Simplicity must also extend to manufacturing, as simpler processes lead to lower costs. Barrier technologies which eschew the two active ingredients required by agonist/antagonist formulations may have the advantage here.

3. **Cost** – The North American experience has shown us that branded ADF products are not easily affordable with prices of US$20 (£15) per tablet and above being commonplace. Such pricing will likely prohibit the introduction of ADFs and their benefits to the European market. In our view, an ADF formulation should cost little more to the payer than a non-abuse deterrent formulation so that access can be assured. As championed by the US FDA, the introduction of value-added ADF bioequivalents to currently marketed products would be a simple first step in providing safer-to-use tablets to patients, without opening the door to excessive pricing, so long as such products were clearly differentiated in their labels. New regulation to ensure any new drug with abuse potential is formulated with abuse deterrent technology from the outset would be a logical follow up, which would enhance and encourage innovation.

THE NEED FOR EFFECTIVE MONITORING – MOSAIC SURVEILLANCE

Effective surveillance is mandatory for effective tracking of any regulatory strategy. In the case of prescription drug abuse, it is needed both to monitor the benefit (or otherwise) of any new ADF product and to track the emergence of new drugs that would benefit from ADF technology to mitigate their abuse potential. Opioids, while a critically important case, are not the only drug that could benefit from an ADF approach. For example, the popular press has recently highlighted abuse of gabapentinoids and benzodiazapines.

In the US pre- and post-marketing surveillance of opioid medications has led to the approval of new products by the FDA and, just as importantly, the removal of products because of their abuse potential.[22] In Europe, however, the lack of such mosaic systems providing accurate, immediately available, geographically relevant, product-specific information is a hindrance both to understanding the extent of abuse in member states and to effective prevention. Multiple input mosaic surveillance systems, for example comprising data streams from the criminal justice system, treatment professionals, susceptible patient populations and acute health events, in parallel with the cost-effective introduction of ADFs, represent an invaluable tool to combat prescription drug abuse and prevent repetition of the North American experience in Europe.

CONCLUSION

Whether or not Europe has an opioid problem may be debated, as Europe lacks the surveillance systems to monitor this adequately. What is clear, however, is that increases in the rates of opioid consumption are tracking those seen in North America and the potential for increased abuse is therefore present and growing. The introduction of ADFs as a preventative measure to mitigate the potential for abuse offers a cost-effective approach to minimise the human and societal costs of abuse. Linked with effective surveillance we believe such measures should be adopted sooner rather than later.

ABOUT THE COMPANIES

Altus Formulation is a Montreal-based pharmaceutical company that invents and develops new enabling technologies and drug products which it then licenses to its various partners around the world. The Altus model is to develop patent protected, safer to use "Value Added Medicines" with a special focus on increased patient access especially in the areas of pain/CNS and oncology.

RADARS® System (Researched Abuse, Diversion and Addiction-Related Surveillance) is a surveillance system that collects product- and geographically specific data on abuse, misuse, and diversion of prescription drugs. Post-market surveillance is performed in the US, Canada, UK, Germany, France, Spain, Italy and other countries.

Recipharm is a leading contract development and manufacturing organisation (CDMO) in the pharmaceutical industry, employing around 5000 people. Recipharm offers manufacturing services of pharmaceuticals in various dosage forms, production of clinical trial material and APIs, and pharmaceutical product development. Recipharm manufactures several hundred different products to customers ranging from big pharma to smaller research and development companies.

REFERENCES

1. *"Prescription opiod overdose data". Centers for Disease Control and Prevention. (www.cdc.gov/drugoverdose/data/overdose.html Accessed Jun 2018)*
2. *Zezima K, Higham S, "Drug executives express regret over opioid crisis, one tells Congress his company contributed to the epidemic". Washington Post, May 2018.*
3. *"Apparent opioid-related deaths". Government of Canada, Mar 2018.*
4. *Dart RC et al, "Trends in opioid analgesic abuse and mortality in the United States". N Engl J Med, Jan 2015, Vol 372(3), pp 241–248.*
5. *"Health at a Glance: Europe 2016 – State of Health in the EU Cycle". OECD and European Commission, Nov 2016.*
6. *van Hecke O, Torrance N, Smith BH, "Chronic pain epidemiology and its clinical relevance". Br J Anaesth, Jul 2013, Vol 111(1), pp 13–18.*
7. *Zimmer Z, Rubin S, "Life expectancy with and without pain in the US elderly population". J Gerontol A Biol Sci Med Sci, Sep 2016, Vol 71(9), 1171–1176.*

8. *Sarganas G et al, "Prevalence, trends, patterns and associations of analgesic use in Germany". BMC Pharmacol Toxicol, 2015, Vol 16, p 28.*
9. *Ruscitto A, Smith BH, Guthrie B, "Changes in opioid and other analgesic use 1995–2010: Repeated cross-sectional analysis of dispensed prescribing for a large geographical population in Scotland". Eur J Pain, Jan 2015, Vol 19(1), pp 59–66.*
10. *Zin CS, Chen LC, Knaggs RD, "Changes in trends and pattern of strong opioid prescribing in primary care". Eur J Pain, Oct 2014, Vol 18(9), pp 1343–1351.*
11. *Abbott TEF et al, "Frequency of surgical treatment and related hospital procedures in the UK: a national ecological study using hospital episode statistics". Br J Anaesth, Aug 2017, Vol 119(2), pp 249–257.*
12. *Feizerfan A, Sheh G, "Transition from acute to chronic pain". Continuing Education in Anaesthesia Critical Care & Pain, Apr 2015, Vol 15(2), pp 98–102.*
13. *Hanks GW et al, "Morphine and alternative opioids in cancer pain: the EAPC recommendations". Br J Cancer, Mar 2001, Vol 84(5), pp 587–593.*
14. *Doleman B et al, "Preventive opioids for postoperative pain". Cochrane Database of Systematic Reviews, Apr 2017, Issue 4.*
15. *"Analgesic use". British Medical Association, Mar 2017*
16. *Greener M, "Will the UK face an opioid abuse epidemic?". Prescriber, Aug 2017, Vol 28(8), pp 36–38.*
17. *Hider-Mlynarz K, Cavalié P, Maison P, "Trends in analgesic consumption in France over the last 10 years and comparison of patterns across Europe". Br J Clin Pharmacol, Jun 2018, Vol 84(6), pp 1324–1334.*
18. *Dunn MK et al, "Overdose and prescribed opioids: Associations among chronic non-cancer pain patients". Ann Intern Med, Jan 2010, Vol 152(2), pp 85–92.*
19. *Green JL et al, "Medical outcomes associated with prescription drug abuse via oral and non-oral routes of administration". Drug Alcohol Depend, Jun 2017, Vol 175, pp 140–145.*
20. *Severtson SG et al, "Sustained reduction of diversion and abuse after introduction of an abuse deterrent formulation of extended release oxycodone". Drug Alcohol Depend, Nov 2016, Vol 168, pp 219–229.*
21. *Dart RC et al, "Do abuse deterrent opioid formulations work?" J Opioid Manag, Nov/Dec 2017, Vol 13(6), pp 365–378.*
22. *"FDA requests removal of Opana ER for risks related to abuse". US FDA News Release, Jun 2017.*

ABOUT THE AUTHORS

Damon Smith, PhD, is the CEO of Altus Formulation, which he founded in 2013. Prior to Altus, Dr Smith held senior research and development positions in biotech and pharmaceutical companies in the UK and Canada.

Richard Dart, MD, PhD, is the Director of Rocky Mountain Poison and Drug Center, Executive Director of the Researched Abuse, Diversion and Addiction Related Surveillance (RADARS®) System, and a professor at the University of Colorado School of Medicine.

Christopher Hirst is Head of RPH Pharmaceuticals AB, a subsidiary of Stockholm-headquartered CDMO Recipharm AB. Mr Hirst has held business development and commercial roles at Recipharm, with a focus on generic and value-added medicines.