Institution: University of Oxford

Unit of Assessment: 4

Title of case study:

Withdrawal of Co-Proxamol: A Successful International Suicide Prevention Initiative

1. Summary of the impact

Research led by Professor Keith Hawton in Oxford starting in 2003 showed that the painkiller co-proxamol ('Distalgesic') was the most common drug used for fatal self-poisoning in the UK. The findings led to its complete withdrawal in the UK by 2008, and further research demonstrated that this was followed by a reduction in deaths from suicide and accidental poisoning. The findings were instrumental in the European Medicines Agency decision in 2010 to recommend withdrawal of the toxic component of co-proxamol, dextropropoxyphene, in all EU countries. This has also occurred in the USA, Canada, and several other countries. The withdrawal of co-proxamol is estimated to have led to approximately 600 fewer deaths by 2012 in the UK alone.

2. Underpinning research

- Co-proxamol ('Distalgesic') is a combination of an opiate, dextropropoxyphene, plus paracetamol. It was a prescription-only painkiller, widely prescribed in the 1980s and early 1990s.

- In a study of local suicides between 1993 and 1997, Hawton and colleagues at the Oxford Centre for Suicide Research noted that co-proxamol was involved in approximately 20% of overdose deaths. Then, using national data on suicide deaths, and local data based on the team's Oxford Monitoring System for Attempted Suicide, Hawton and colleagues showed in a key paper published in the *British Medical Journal* in 2003 that: (a) co-proxamol was the most common drug used for suicide in England and Wales (18%; 766 out of 4162 fatalities), and (b) the risk of death following an overdose of co-proxamol was 28 times greater than that for paracetamol (Hawton, Simkin and Deeks, 2003). It was this study which prompted the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Committee for the Safety of Medicines (CSM) to investigate the safety of co-proxamol in 2004.

- In parallel, the Hawton research team conducted a study in 24 coroners' jurisdictions of 123 people who died from co-proxamol overdose to determine the characteristics of these individuals and the circumstances of their suicidal acts (Hawton, Simkin *et al.*, 2005). This showed that in over 80% of cases the co-proxamol had been prescribed for the individual (rather than someone else) and that death sometimes resulted from relatively small overdoses. The team also conducted a review of the international research literature on co-proxamol poisoning (Simkin, Hawton *et al.*, 2005). This showed that the majority of deaths occurred before individuals reached hospital. Based on the data, they proposed that '*complete withdrawal [of co-proxamol] should be considered'*. This was the first time that this course of action had been proposed.

- The Oxford team contributed to the MHRA/CSM review of the benefits and risks of co-proxamol mentioned above, both by giving evidence and participating as advisors. The conclusion of the review was that the MHRA recommended to the CSM that co-proxamol should be withdrawn in the UK. This recommendation was implemented: there was an initial withdrawal phase between 2005 and 2007 when no new patients were prescribed co-proxamol, followed by full withdrawal of the drug in 2008.

- Hawton and colleagues showed that as prescriptions for co-proxamol markedly declined during the withdrawal phase (2005-7), there was a corresponding reduction in deaths due to poisoning with the drug (Hawton, Bergen *et al.*, 2009) and also fewer non-fatal poisonings (Hawton, Bergen *et al.*, 2011). Encouragingly, there was no substantial increase in poisoning deaths involving other analgesics used in place of co-proxamol.

- More recently the research team have evaluated the longer-term impact of the initiative, including following full withdrawal of co-proxamol from 2008 to 2010 (Hawton, Bergen *et al.*, 2012). This showed a similar picture, with a further decrease in deaths due to co-proxamol poisoning, such that over the six-year period from the beginning of the initial withdrawal there were about 600 fewer deaths, with again no indication that deaths due to overdoses with other analgesics increased significantly.

3. References to the research

Hawton K, Simkin S, Deeks JJ. Co-proxamol and suicide: a study of national mortality statistics and local non-fatal self-poisonings. *BMJ*. 2003;326:1006-8. DOI: 10.1136/bmj.326.7397.1006

Demonstrated the extent to which co-proxamol contributed to suicide poisoning deaths and toxicity of co-proxamol relative to other drugs used for self-poisoning. 42 citations.

Hawton K, Simkin S, Gunnell D, Sutton L, Bennewith O, Turnbull P, et al. A multicentre study of co-proxamol poisoning suicides based on coroners' records in England. *Br J Clin Pharmacol*. 2005;59(2):207-12. DOI: 10.1111/j.1365-2125.2004.02252.x

Identified characteristics of people dying by suicide using co-proxamol poisoning, including fact that death could result from relatively small overdoses. 26 citations.

Simkin S, Hawton K, Sutton L, Gunnell D, Bennewith O, Kapur N. Co-proxamol and suicide: a review to inform initiatives to prevent the continuing toll of overdose deaths. *Q J Med* 2005;98:159-70. DOI: 10.1093/qjmed/hci026

Highlighted international problems and concerns regarding co-proxamol poisoning. 17 citations.

Hawton K, Bergen H, Simkin S, Brock A, Griffiths C, Romeri E, et al. Effect of withdrawal of co-proxamol on prescribing and deaths from drug poisoning in England and Wales: time series analysis. *BMJ*. 2009;338:b2270. DOI: 10.1136/bmj.b2270

Showed large initial beneficial impact of withdrawal of co-proxamol on poisoning suicides and accidents, without compensatory increase in deaths involving other analgesics. 28 citations.

Hawton K, Bergen H, Waters K, Murphy E, Cooper J, Kapur N. Impact of withdrawal of the analgesic co-proxamol in the UK on non-fatal self-poisoning. *Crisis*. 2011;32(2):81-7. DOI: 10.1027/0227-5910/a000063

Demonstrated similar benefits regarding non-fatal poisonings. 4 citations.

Hawton K, Bergen H, Simkin S, Wells C, Kapur N, Gunnell D. Withdrawal of co-proxamol in England and Wales: time-series investigation of impacts on prescribing and deaths during the six years after the withdrawal. *PLoS Medicine*. 2012;9: e1001213. DOI:10.1371/journal.pmed.1001213

Showed longer-term benefits of withdrawal of co-proxamol on suicidal and accidental poisoning deaths. 4 citations.

Professor Hawton led research in Oxford on suicide prevention throughout this period, in his role as Director of the Centre for Suicide Reseach at Oxford University. He is also an honorary consultant psychiatrist. Key colleagues on the research included Sue Simkin, Helen Bergen, and John Deeks, and collaborators Nav Kapur (Manchester) and David Gunnell (Bristol).

Details of peer reviewed grants and fellowships that supported this work:

Hawton (PI) 2003-2008 *Department of Health* (£379,421) Oxford Monitoring System for Attempted Suicide

Hawton (PI) 2002-2004 *Department of Health* (£122,055) Coroner-based Investigation of Specific Methods of Suicide

Hawton (PI) 2004-2010 *Department of Health* (£1,757,022) Multicentre Study of Self-harm in England
Hawton (PI) 2007-2011 *National Institute for Health Research* (£897,994) A multicentre programme of clinical and public health research in support of the National Suicide Prevention Strategy for England
Hawton NIHR Senior Investigator Award (fellowship award from NIHR 01/4/09 – 31/03/14)

4. Details of the impact

- As highlighted above, the research of Hawton and colleagues was instrumental in leading to the withdrawal of co-proxamol (and its toxic component dextropropoxyphene) in the UK from 2005 onwards (Section 5, Sources 1-5).

- The resulting benefits were shown during the initial three year withdrawal phase (2005-7) in terms of a major reduction in deaths, both suicidal and accidental, from co-proxamol poisoning and absence of significant increases in deaths involving other analgesics likely to have been prescribed instead of co-proxamol. (See Hawton et al, 2009, 2011, cited in Section 3).

- More recently the long-term benefits of this initiative have been demonstrated through evaluation of its impact during the six years 2005 – 2010, including the three years following full withdrawal. This has indicated about 600 fewer deaths in the UK from co-proxamol poisoning and again no major substitution of deaths from fatal poisoning with other analgesics. (See Hawton et al, 2012, cited in Section 3).

- This initiative has been one of most important contributions to the success of the National Suicide Prevention Strategy for England (see Section 5, Sources 1-3).

- This initiative did not stop in the UK. Following presentation of the Oxford team's findings by Hawton to the European Medicines Agency (EMEA), the EMEA recommended to the European Union (EU) that non-prescribing of dextropropoxyphene should become policy throughout the EU. The decision was endorsed in June 2010. (Section 5, Source 6).

- The UK and EU initiative prompted the US Food and Drug Administration to take action in 2010 to withdraw dextropropoxyphene in the USA. (Section 5, Source 7).

- In 2010 Health Canada did likewise in Canada, as did the equivalent authorities in New Zealand, Singapore and Taiwan (Section 5, Sources 8-10). Thus it is anticipated that the work of Hawton and his team will contribute to the saving of lives in many countries, not just in the UK.

5. Sources to corroborate the impact

1. Letter from MHRA Director, Dr June Raine, in August 2012, confirming importance of Hawton's research in the decision to withdraw co-proxamol. Includes the statements: '*Your research team's contribution has been pivotal'* and '*…one of the most significant public health actions of the last decade…'* Available on request.

2. Letter from Professor Louis Appleby, former Director of Mental Health for England, and Chair of the National Suicide Prevention Strategy Group for England, confirming importance of Hawton's research on co-proxamol (and his other research on suicide prevention). Includes the statements: *'His work on suicide by co-proxamol overdose has led to the withdrawal of this drug and a substantial reduction in suicides by this method, without a compensatory increase in suicide using other analgesics…*' and *'…findings from Prof Hawton's research have been and remain highly influential*.' Available on request.

3. The renewed National Suicide Prevention Strategy (2012) states (page 38): '*Significant*

progress has been made in reducing access to medications associated with suicide attempts, including the phased withdrawal of co-proxamol…,' citing the Hawton et al. 2012 PLoS Medicine paper (cited in Section 3 above) to support this conclusion. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216928/Preventing-Suicide-in-England-A-cross-government-outcomes-strategy-to-save-lives.pdf [Accessed 4/11/13]

4. Medicines and Healthcare products Regulatory Agency. Withdrawal of co-proxamol products and interim updated prescribing information CEM/CMO/2005/2. 2005 [updated 2008/07/09/02/03/2005]; http://www.mhra.gov.uk/home/groups/pl-a/documents/websiteresources/con019461.pdf [Accessed 4/11/13]. Highlights the Hawton et al. 2003 BMJ paper (cited in Section 3 above) as being the evidence behind the decision.

5. Committee on Safety of Medicines. Withdrawal of co-proxamol (Distalgesic, Cosalgesic, Dolgesic). *Current Problems in Pharmacovigilance*. 2006;31(May):11. http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con2023860.pdf [Accessed 4/11/13]

6. European Medicines Agency (EMEA) recommends withdrawal of dextropropoxphene-containing medicines (including co-proxamol). (http://www.mhra.gov.uk/NewsCentre/CON049300 [Accessed 4/11/13]). This announcement highlights Hawton's research.

7. FDA U.S. Food and Drug Administration. Xanodyne agrees to withdraw propoxyphene from the U.S. market. 2010 [updated 01/12/201015/05/2011]; Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm234350.htm. [Accessed 4/11/13]

8. Health Canada. Darvon-N (dextropropoxyphene) - Recall and Withdrawal in Canada - For the Public. 2010 [cited 2011 11/05/2011]; Available from: http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2010/16115a-eng.php [Accessed 4/11/13]

9. Withdrawal in New Zealand: http://www.medsafe.govt.nz/hot/alerts/dextropropoxyphene.asp [Accessed 4/11/13]

10. Withdrawal in Singapore: http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/product_safety_alerts/safety_alerts_2009/suspension_of_sales.print.html?Status=1 [Accessed 4/11/13]