RWE THOUGHT EXPERIMENT: COULD RWE HAVE PREVENTED TODAY'S OPIOID EPIDEMIC? LESSONS FROM 19TH CENTURY CHINA

Sheila Mahoney MBA, LifeSciHub LLC, William John, MD, Duke Medical School, Luo Zhou, Chinese Studies Librarian Duke University Libraries, Durham, NC 27708

INTRODUCTION

Objective: Thought experiment to assess how Real World Data/Evidence (RWDE) could have played a role in assessing modern day addiction liability of pharmacotherapeutics. Data presented highlighting RWD from the opium epidemic in 19th century China to 21st century opioid epidemic in the U.S.

This thought experiment seeks to answer 3 fundamental questions:

1. Opioid crisis in 19th century China is unquestionably data, but was it Real World Evidence (RWE)? Why/why not?
2. Historical sources will be mined for data points to parallels between 19th Century China and today's opioid epidemic. Could these have been used as predictive indicators?
3. Consideration of the temporal nature of data- if we, today, reject all data generated outside of present moment commonly held data and technology standards, what will happen 50 years from now, looking back on data from today?

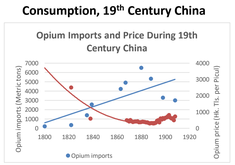
Question 1: 19th Century China- RWE?

Table 1. Controls for Common Biases Associated with Retrospective Observational Studies

	Selection bias[4,5]	Adjustment for Causal Intermediates[4,5]
Survivorship Bias, also known as Depletion of Susceptibles, applies to all studies. This is the tendency to focus on people, things or data that successfully passed a selection process, overlooking those that did not, typically because of their lack of visibility to those analyzing the information.[4] Although frequently mentioned descriptively, no reliable, quantifiable mortality was identified in the 19th century data set.	A systematic error in creating intervention groups, causing them to differ with respect to measured or unmeasured baseline characteristics, and ultimately prognosis	Adjusting for variables on the causal pathway between treatment and outcome can result in biased estimation of both the total effect of treatment and the direct effect that is not mediated through the adjustment variables
1a. Provinces Survey 16 of the 18 provinces reported "impartial attempt to estimate the quantities of opium…consumed during the years 1906 and 1908, respectively. Reporters were either province or city level commissioners, or Port Medical Officers.	• No evidently standard criteria used to gauge opium use, or standardized training provided to observers to ensure questions asked in the same way. (1a, b, c.) In study 2, Investigators (survey respondents) were European trained MDs, average of 9 years, range of 1-44 years in country, with observational opportunities- aggregate of over 750,000 patients seen per year (considered an underestimate). • No specific description of "methods or directions." 1b,c • Study 2: Evident bias in association name: "Anti-Opium League". Study design considerations: Some attempt at standardizing questions: 18 questions based on the questions asked by the Royal Opium Commission. However, no standardized answers, which ranged from quantitative (percentages and ranges) to free text (some, few, many, most). Except where noted only quantitative data were analyzed. If a range was given as was common, such as 50-60%, the difference was used for analysis (55%).	• Were officials politically incentivized to over report or under report? (1a, b, c.) • Frequent mention of differing levels of use in cities and villages: more, less, respectively. (1a, 2) • No evident control for survey respondents' level of honesty in answers. Were there factors that would cause a respondent to answer no when in fact the answer was yes? + • Although not quantified, frequent mention of consumption in all social classes, therefore no adjustment made based on class. (1a, b, c, 2)
1b. Szemao Quantitative Study In 1908 in Szemao, a city with a population of 4,109, the Commissioner of Customs conducted a house to house survey to determine opium use.		
1.c Nanning Use and Severity In 1907 in Nanning, a city with an adult, non-military male population of 21,411 (official census data), used "careful inquiry pursued in many directions and by various methods" to measure opium consumption and severity.		
2. 100 Physician's Opinions Soochow Missionary and Literary Association formation of Anti-Opium League in China, answered by both foreign missionary and Chinese physicians, Originally expected 60 responses, received over 100 (total number surveyed not provided).		

+ For so long as opium is so readily obtainable as it is, and doubtless will continue to be for a long time to come, the average smoker will probably refuse, from one motive or other, to admit that he is addicted to a habit [1]

Tables 2a,b. Imports, Price and Consumption, 19th Century China



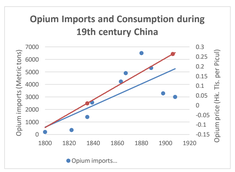


Table 3. Use and Severity- 19th Century China[1]

1c. Nanning				Adult Males		
100 Physicians [3]	DSM-5[2]	Nanning Com. Of Customs Use Description	Count	Smokers		Total Adult Males
"Opium Sots"	Opioid Use Disorder	Deeply seated	400	2200	55%	10%
		Committed	1200			
		Craving	600			
		Moderate	1800	1800	45%	8%

1a. Provinces	
Av Opium Use	25%
Median	20%

1b. Szemao Smokers		
Male	529	26%
Females	83	4%

2. 100 Physicians

What are the proportions of those who smoke opium	Av.	Median
A. Without injury?	4%	0%
B. With slight injury?	38%	30%
C. With great injury? ("opium sots")	56%	50%

METHODS

We reviewed historical sources to identify quantitative and qualitative reports on opium and opium-related problems in 19th century China, and selected several that could qualify as retrospective observational study design. For analysis, qualitative descriptions were not included (some, many), when quantitative ranges were provided (50-60%) the average was used for calculation (55%).

Study populations varied. Except where noted (1b) all 19th century data were for adult males, and were considered to represent the general population, with class and other considerations addressed in Table 1. Historical data mentioned race and ethnicity but too rarely to allow for analysis and comparison. Modern data represented general population.

RWE Techniques used to control for bias addressed in Table 1. We identify three biases common to retrospective observational studies: Selection Bias, Survivorship Bias, and Adjustment for Causal Intermediates.

CMC: no analysis was conducted comparing drug composition or potency between the time periods, although this could be interesting for further study.

Both time periods admit to non-controlled use and inability to measure the black market, therefore officially reported data is used as the sole measure of consumption and impact for both periods.

Question 2: Parallels of Modern Use

Table 4. Diagnoses Comparison: 2013[2], 1899[3]

DSM 2013	Physician Survey 1899
1. Opioids are often taken in larger amounts or over a longer period than was intended.	Is there a tendency to increase amount smoked? 95-yes, 0-no, 7 no answer. "The initial effect is soon lost unless increased"
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.	It seems to be just within the bounds of possibility that a man can or may free himself of the habit, but such an one is undoubtedly a "rara avis"
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.	When the habit becomes inveterate, it is necessary to smoke at certain fixed hours. Time is consumed, men's duties are forgotten.
4. Craving, or a strong desire or urge to use opioids.	When night comes in gloom, he seeks again the sorceress into whose power he has sunk, and whose finger mocks as it beckons him on.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.	He cannot turn his thoughts to his calling, he is unfit for exertion, his days pass in sloth and bitter remorse.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.	A fearful desolating pestilence, pervading all classes of people, wasting their property, enfeebling their mental faculties, ruining their bodies and shortening their lives.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.	A confirmed opium smoker is never fit to conduct business, and generally unfit for all social intercourse with his friends and family.
8. Recurrent opioid use in situations in which it is physically hazardous.	No evidence of this criteria.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.	People perceive that it hurries them to destruction, but it leaves them without spirit to desist.
10. Tolerance, as defined by either of the following: a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect. b. A markedly diminished effect with continued use of the same amount of an opioid. Note: This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.	At first he cannot inhale more than from 3 to 6 grains at a time, but will go on gradually increasing the dose, till in a few years some will consume even 300 grains daily.
11. Withdrawal, as manifested by either of the following: a. The characteristic opioid withdrawal syndrome (refer to Criteria A and B of the criteria set for opioid withdrawal). b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.	If the dose be not taken at the usual time, there is great prostration, vertigo, torpor, and discharge of water from the eye…coldness is felt over the whole body, with aching pains in all parts. Diarrhea occurs, the most horrid feelings of wretchedness come on, and if the poison be withheld, death terminates the victim's existence. Restlessness, wakefulness, yawning and stretching, and lachrymation. On second or third day, general distress shews itself by patient twisting and curling about, as if he could find no posture easy. Will often curl himself up in a kneeling attitude, beat his bed, etc. Diarrhoea, dysentery, cough, and some dyspnoea may all show themselves in different patients. Such will break any rule to get opium if they possibly can. These symptoms are much worse on the third or fourth day, after which they slowly become less marked. I consider dysentery the most unfortunate symptom produced, though not the most common.

Table 5. 2015 Use, Misuse, Disorder as Percent of US Population [8]

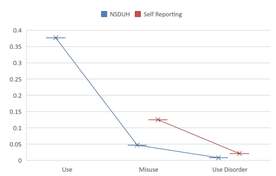
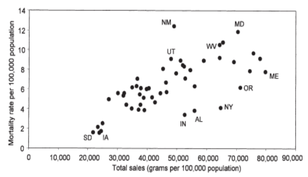


Table 6. Total opioid analgesic sales versus unintentional and undetermined drug poisoning mortality rates by state, United States, 2002[7]



RESULTS

We found striking similarities of opioid use and effects reported in both time periods:

On data quality:

- In 1909 we found evidence of data quality checking and review amongst different officials and entities. All reported difficulty in obtaining exact numbers. The main method was surveys. "The Chinese delegates trust, therefore, that the Commission will accept the estimate given in the Memorandum, which was purposely put down at the lowest possible figure". Likewise in 2017, "data on the prevalence of prescription opioid use, misuse, and use disorders are limited."[8]

On Data Variation

- The Provinces study (1909), observed great variation depending on region: "1/3 of the adult male population are addicted to the vice"; the number of smokers at Kiaochow is roughly estimated at 2,200 out of a total population of 44,400, or 5 percent". Paulozzi (2006) also found "there was over a ten-fold variability in sales of some opioid analgesics" across the United States.

On Beginning Opioid Use:

- 2017: The most commonly reported motivation for misuse was to relieve physical pain (63.4%) [8]
- 1899: Percentage that began for some ailment (57.75%)[2]

On Diagnosis

- Although described in distinctly different language styles than modern day, Table 4 shows clear correlation of 1899 MDs with modern criteria for Opioid Use Disorder, with one exception (8).

On Consumption

- Table 3 presents several studies conducted by the Opium Commission of 1909, which concluded that 23.33% of the adult male population was addicted to opium. In 2015 US population misuse, Table 5, reported at 4.7% by the National Survey on Drug Use and Health, and higher, self reported 12.5% misuse. No conclusions were drawn about consumption due to confounding factors such as access and controls- although 19th Century China issued smoking licenses as some means of official control, those were known to be not at all representative of consumption, and not comparable to the modern-day restriction of prescriptions.
- Tables 2a,b together show availability of opium and the impact on consumption. Although measuring 2015 opioid mortality, not consumption, in Table 6, a similar upward trend is clear regarding drug exposure (imports and prescriptions, respectively).

CONCLUSIONS

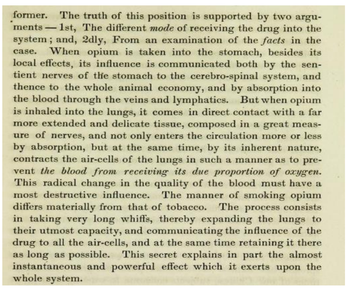
Trends such as exposure, consumption, reasons for beginning, diagnoses of the medical community, all serve as evidence that the experiences of 19th Century China were indeed potential predictors of the modern day opioid epidemic. Perhaps the most striking evidence is shown in Table 7, showing FDA's reliance on dosage form, i.e., controlled release as the primary means of preventing abuse. Next to Table 7 it is an 1899 MD's description of what happens when opium use goes from oral ingestion, the most common means of consumption in other regions such as India, Persia, Turkey and Great Britain, where the opium crisis was far less than China on an order of magnitude, to inhalation. Clearly, the best train physicians at the time knew of the danger and could describe it in startlingly accurate, medical detail.

The authors conclude that with RWE, perfect is the enemy of good. Just because the patient experience pre-dated the advent of formal medical records and spreadsheets should not render it obsolete. Data is big in 2022 and only getting bigger. Our means of taking measurements are getting ever more sophisticated. We as an industry, and a society, must find a way to ensure that specificity doesn't breed arrogance, such that valid human experiences are forgotten in the dust of history.

Our second conclusion is that the dominant bias that impacted the ability to utilize these RWD to prevent the modern opioid epidemic is familiar to the medical community, and is confounding indeed: patients have agency. Although only slightly represented here, the information provided by qualified 19th century officials is so alarming, we believe that, had it been included in some form in the regulatory process, it may have proven the risk to be so high as to overcome the patient agency bias and prompted further safety study.

Table 7. Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse

At the time of approval, FDA believed the controlled-release formulation of OxyContin would result in less abuse potential, since the drug would be absorbed slowly and there would not be an immediate "rush" or high that would promote abuse. In part, FDA based its judgment on the prior marketing history of a similar product, MS Contin, a controlled-release formulation of morphine approved by FDA and used in the medical community since 1987 without significant reports of abuse and misuse.[6]



former. The truth of this position is supported by two arguments — 1st, The different *mode* of receiving the drug into the system; and, 2dly, From an examination of the *facts* in the case. When opium is taken into the stomach, besides its local effects, its influence is communicated both by the sentient nerves of the stomach to the cerebro-spinal system, and thence to the whole animal economy, and by absorption into the blood through the veins and lymphatics. But when opium is inhaled into the lungs, it comes in direct contact with a far more extended and delicate tissue, composed in a great measure of nerves, and not only enters the circulation more or less by absorption, but at the same time, by its inherent nature, contracts the air-cells of the lungs in such a manner as to prevent *the blood from receiving its due proportion of oxygen.* This radical change in the quality of the blood must have a most destructive influence. The manner of smoking opium differs materially from that of tobacco. The process consists in taking very long whiffs, thereby expanding the lungs to their utmost capacity, and communicating the influence of the drug to all the air-cells, and at the same time retaining it there as long as possible. This secret explains in part the almost instantaneous and powerful effect which it exerts upon the whole system.

3

REFERENCES

1. China. *Report of the International Opium Commission, Shanghai, China, February 1 to February 26, 1909, Volume 2 Reports from the Delegations, China Report Section IV: Consumption of Opium, pages 62-66.* Shanghai, China. North-China Daily News & Herald, Ltd. 1909.
2. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.). DSM-5 Criteria for Diagnosis of Opioid Use Disorder, page 541.
3. Park, William Hector. Opinions of Over 100 Physicians on the Use of Opium in China. Shanghai: American Presbyterian Mission Press; 1899.
4. Taur SR. Observational designs for real-world evidence studies. Perspect Clin Res. 2022;13(1):12-16. doi:10.4103/picr.picr_217_211.
5. FDA. Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products, Draft Guidance for Industry, September 2021
6. FDA. Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse, April 1, 2022
7. Paulozzi LJ, Ryan GW. Opioid analgesics and rates of fatal drug poisoning in the United States. Am J Prev Med. 2006;31(6):506-511. doi:10.1016/j.amepre.2006.08.017
8. Han B, Compton WM, Blanco C, Crane E, Lee J, Jones CM. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. Ann Intern Med. 2017;167(5):293-301. doi:10.7326/M17-0865
9. Lodwik Kathleen L. Crusaders Against Opium: Protestant Missionaries in China, 1874-1917. University Press of Kentucky, 2014.