Optimization of the Production of Lofexidine
(Technical Paper)

Implementation of Tactics Employed by the European Union to Reduce Rates of Antibiotic Consumption and Resistance
(STS Paper)

A Thesis Prospectus in STS 4500
Presented to the Faculty of the School of Engineering and Applied Science
University of Virginia • Charlottesville, Virginia
In Partial Fulfillment of the Requirements of the Degree
Bachelor of Science, School of Engineering

Author
Christian Mcilvenna
Fall, 2019

Technical Project Team Members
Julia Andreozzi
Daniel Lim
Nicholas Malmgren
John Nguyen

On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

Signature _____ Date _____
Christian Mcilvenna

Approved _____ Date _____
Eric Anderson, Department of Chemical Engineering

Approved _____ Date _____
Thomas Seabrook, Department of Engineering and Society

Background and Overview of Thesis Components

Rampant overuse of synthetic pharmaceuticals has precipitated a number of public health emergencies across the globe. In the United States, the opioid abuse crisis has continued to expand every year with no sign that growth will slow. In 2017, over forty-five thousand Americans lost their lives to opioid overdoses. Increases in opioid abuse mortality are vastly outpacing U.S. population growth, with the specific death rate doubling between 2000 to 2010 and yearly growth reaching a high of 20% in 2016 (Rudd, Aleshire, Zibbell, & Gladden, 2014; Scholl, Kariisa, Wilson, & Baldwin, 2018). Even after prescription volumes have been reduced, threats of withdrawal and relapse persist for those already afflicted by opioid usage. Nearly all drugs for treatment of opioid withdrawal are addictive opioids themselves; a conundrum befalls those on the road to recovery (Rehman et. al., 2019).

In Europe and Asia, infectious diseases are steadily becoming more dangerous as a rising number of medications lose effectiveness against bacteria. By the end of the 20th century, European Union countries had begun to understand the broad scope of damages that could result from the spreading of drug-resistant bacteria and had taken localized steps to monitor and mitigate the issue (Bronzwaer, Lönnroth, & Haigh, 2004). Beginning in 2011, the EU drafted a bloc-wide action plan to deal with drug-resistant bacteria after these localized efforts were seen as insufficient. Shortly after, a worldwide action plan was published by the World Health Organization which prompted an adjustment of the EU plan to the most recent version ("Global action plan on antimicrobial resistance", 2015; "EU Action on Antimicrobial Resistance", 2017). Despite high income countries successfully leveling or reducing antibiotic consumption since 2011, global consumption has increased by 39% in 15 years. This discrepancy is due to antibiotic usage spiking among low-middle income countries (Klein et. al., 2018).

The technical project will address the need for a non-addictive medication to treat opioid abuse by optimizing the production of Lofexidine, the only FDA-approved medication for opiate withdrawal symptoms that is not an opioid. The research paper will assess feasibility of potential methods for managing ramifications associated with an outburst of antibiotic consumption in lower income countries (which are more vulnerable to drug-resistant bacteria). The assessment will be based on analysis of social and technical infrastructure necessary to implement existing stratagems used by the European Union for curtailing antibiotic consumption and resistance.

Application of Lofexidine to the Opioid Crisis

Addiction often persists for years before serious health problems become apparent. Increases in the rate of hospital visits due to opioid misuse and inquiries into addiction treatments consistently rise faster than morbidity (Kolodny et al., 2015). Debilitating symptoms from halting drug usage (withdrawal) are a significant driver of addiction. Understanding the economic burden of adverse health outcomes is essential when considering cost-effective prevention strategies. The U.S. economic burden -- including healthcare and substance abuse treatment cost, criminal justice and cost productivity -- was estimated to be over $78.5 billion in 2013 (Florence, Zhou, Luo, & Xu, 2013). This technical project focuses on scaling up the production of the opioid withdrawal medication Lofexidine with the aim of lowering manufacturing costs and Lofexidine prices.

Before Lofexidine, a majority of the recommended medications for management of opiate withdrawal were other opioids with methadone and buprenorphine-naloxone being the most common (“FDA Briefing Document”, 2018). The propensity of patients struggling with opiate addiction to become addicted to these medications necessitated a non-addictive product

for withdrawal management. Lofexidine is a non-opioid, alpha-2-adrenergic agonist prescription medication that works to block the release of norepinephrine, a hormone responsible for many of the most frequently experienced withdrawal symptoms. Clinical studies have shown that withdrawal symptoms are resolved sooner with lofexidine compared to tapered dosing of methadone, resulting in a shorter treatment period (Wakeman, 2018). Data collected on 1,074 opiate detoxifications conducted with lofexidine in the United Kingdom showed successful results in more than 60% of the subjects at a mean of 10 days of detoxification (Akhurst, 1999), further demonstrating the effectiveness of lofexidine in a short timescale.

Lofexidine was first sold in the United Kingdom to treat opiate withdrawal symptoms under the name Britlofex in 1992. However, doubts concerning the drug's effectiveness and value compared to its main competitor (clonidine) delayed the U.S. from considering the medicine until a more substantive clinical study was submitted in 2016 (Rehman et al., 2019). FDA approval quickly followed in 2018, allowing Lofexidine to be marketed under the name Lucemyra. Despite the fast track approval, Lofexidine has not attracted much attention in the U.S. because generic clonidine is much cheaper and marketing has generally failed to entice investors (Solorio, 2018). Moreover, the drug's availability in the UK has suffered a sharp decrease since May 2018 due to manufacturing issues; supplies could not be imported from the other two principal manufacturers, China and the U.S. (Erskine, 2018). In the absence of new medications for opiate withdrawal, the market for lofexidine production will likely expand to Canada and other EU countries where it has been approved (Vartak, 2014).

Optimization of a Chemical Process for Production of Lofexidine

The technical project will analyze all necessary details for the effective scaleup of a five step process authored in 2008 for synthesis and isolation of lofexidine from enantiopure methyl

lactate and 2,6-dichlorophenol, outlined in *Figure 1* (Crooks & Vartak, 2012). As an overview, the starting material, an enantiomer of methyl lactate, is reacted with 2,6-dichlorophenol, triphenylphosphosphine, and diisopropyl azodicarboxylate to create 1-methyl-1-[2,6-dichlorophenoxy]ethanoate. Next, the 1-methyl-1-[2,6-dichlorophenoxy]ethanoate is converted to 1-methyl-1-[2,6-dichlorophenoxy]ethanamide through treatment with ammonia. The third step of the synthesis involves the conversion of 1-methyl-1-[2,6-dichlorophenoxy]ethanamide to an imino-ether intermediate through an electrophilic attack by a trimethoxonium ion to the amide oxygen, and further converting the intermediate to 2-[1-(2,6-dichlorophenoxy)-ethyl]1,3-diazacyclopent-2-ene by adding ethylene diamine. Finally, the resulting product can be converted into a pharmaceutically functional acid salt through treatment with aqueous hydrochloric acid.

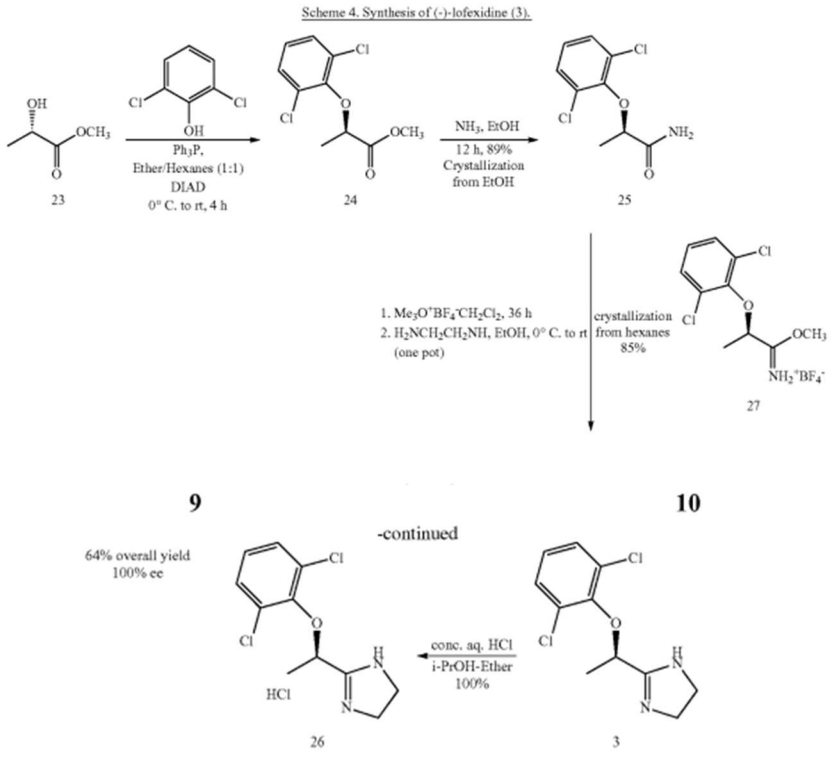

Figure 1. Proposed Five-Step Synthesis Process of Lofexidine for Scale-Up (Crooks & Vartak, 2012)

As illustrated in Figure 1, the process incorporates three low temperature reactions and two crystallizations; five apparatuses will be necessary to design for high rates of production. However, the proposed synthesis is more efficient than other proposed mechanisms as it does not require additional purification techniques such as distillation or column chromatography. Furthermore, the desired product is returned at a yield of roughly 64% - roughly triple that of the next best proposed synthesis (Crooks & Vartak, 2012).

The technical report will be produced in the form of a chemical process facility schematic which a prospective manufacturer could use for a preliminary cost/benefit analysis. The facility outline will include all necessary raw material costs, product revenues, waste disposal methods, utility requirements, installation expenses, and equipment details. Each of the four team members will contribute to all major aspects of process development. Due to resource limitations, testing of equipment designs and specifications will be executed in Aspen Plus Version 11. Financial evaluations will incorporate estimates of equipment installation and waste management costs from handbooks such as Turton (2018), operational power requirements from the Aspen software, and a competitive price for the drug based on the Chinese sale price of roughly $1,776 for 84 tablets lasting the initial seven day treatment period (Bryce, 2019). A design basis memorandum will be formulated in December 2019 to address production goals and safety concerns. The full process design will be finished by March 2020, followed by a comprehensive economic appraisal in April to precede the completed technical report.

Risk Society as a Framework for Antibiotic Consumption

Ulrich Beck's framework of "risk society" will be used to compartmentalize the decisions made by legislatures surrounding the production and usage of antibiotics. Risk society

incorporates the principle of "reflexive modernity," in which societies' widescale production initiatives backfire and they must deal with the consequences (Wimmer & Quandt, 2006). Beck describes a risk society where "a threatening future, still contrary to fact, becomes the parameter of influence for current action" (Adam, Beck, & Loon, 2000, p. 222). This framework seems especially applicable to Antimicrobial Resistance (AMR) which was an unforeseen consequence of a global initiative to improve quality of life. Antibiotics were overused without foresight when governments assumed new antibiotics could be developed to meet rising demands; the slow progress of novel antibiotic research has forced modern societies to change course and preserve antibiotic usefulness.

Critics of risk society theory have argued that greed and ignorance undermine risk planning more effectively than consequences can force it. Stakeholders with economic power can easily dissuade politicians from addressing risks and limit the ability of consumers to understand risks. Beck's indication that free markets will eventually shift to accommodate known risks in the absence of official policy may be true in a sense; critics will argue that the public might still ignore recognized risks if there are no images associated with these risks which evoke fear (Ormrod, 2013). While drug-resistant bacteria do not kill as often as opioids *right now*, public health organizations in the UK have painted a sobering picture where drug-resistant bacteria could kill hundreds of millions of people and cost the world economy hundreds of trillions of dollars by the turn of the century (O' Neill, 2016). The risk society framework will test how effective such predictions have been at inducing motivation to fight the AMR crisis among legislative bodies and private citizens.

Implementation of Tactics Employed by the European Union to Reduce Rates of Antimicrobial Consumption and Resistance

Individual EU member states had begun to take actions against the oncoming threat of AMR by 1995. In 1999, the European Commission attempted to unite these damage control efforts by drafting a consolidated strategy for the bloc. This plan identified four major areas for legislative action: research/development, surveillance, prevention, and containment (Bronzwaer et. al., 2004). However, meaningful progress has only been made in the latter three areas. Antibiotic developments in the 21st century have mostly produced compounds with minor differences to previously existing antibiotic classes; research into attacking resistance mechanisms has been even less fruitful (Lopatkin et. al., 2017; Nicolas et. al., 2019). Alternative treatments in the form of vaccines and bacteriophages have shown promise, but their coverages are often too narrow to constitute significant progress against the aggregate threat (Henriques-Normark & Normark, 2014; Bragg et. al., 2014).

Surveillance involves monitoring both the consumption of antibiotics and the effectiveness of antibiotics at stopping individual diseases. A wide surveillance network allows growth and transmissions of drug-resistant bacteria to be tracked effectively as they proliferate across the globe. The primary AMR surveillance system for the EU (EARS-Net) currently consolidates information from over 50 public health organizations ("About the Network", 2012). In an effort to establish a surveillance network with wider reach, World Health Organization has consolidated action plan information and preliminary data from 86 countries since 2015 (mostly in Europe, Africa, and Asia). Central and South American regions appear to be relatively uninvolved, with only three countries submitting any documents ("Country Participation", 2019). Perceived lack of interest suggests these regions are currently the least affected by AMR and stand to benefit the most from preemptive planning.

Prevention will become the most important aspect of crisis mitigation as the situation unfolds; research has shown that limiting antibiotic usage does not slow resistance propagation after resistance among bacterial populations reaches a certain threshold (Lopatkin et. al., 2017). Urbanization in low-middle income countries greatly exacerbates the problem, as crowding in unequipped areas leads to increased disease transmission. Higher disease rates may precipitate a rise in antibiotic consumption which strengthens AMR (Alirol et. al., 2011; Bruinsma et. al., 2003). In a locality where sanitation programs are not sufficiently developed, the most applicable AMR prevention methods are educational. Education is used to reinforce proper protocols for antibiotic application so insufficient and unnecessary dosages can be avoided (Bronzwaer et. al., 2004). Though it may be difficult to inform the general public in low income countries, improving guidelines for healthcare providers is significantly worthwhile (Huttner & Harbarth, 2009).

Containment primarily concerns maintaining the effectiveness of specific antibiotics as long as possible; usefulness degrades when antibiotics are used in uncommon fashion or the manufactured quality of common antibiotics is poor (Fries, 2004). The food industry is most involved in containment procedures, as animals are estimated to consume more total antibiotics than humans in many countries across the income spectrum (Van Boeckel et. al., 2015). Unless massive support for plant-based diets negates a rapidly increasing demand for animal products, sustained regulations on animal antibiotic usage are crucial – specifically limits on animals' reception of antibiotics designated essential for human safety (Maron, Smith, & Nachman, 2013).

The research paper will consist of two main sections; one will address effectiveness of actions taken by the EU at slowing antimicrobial consumption and resistance propagation, and the other will discuss adaptability of these tactics based on a country's income level. Each section will be divided into three parts for detailing surveillance, prevention, and containment

measures. A preliminary outline for the research paper will be formulated in late January after an initial round of readings starting January 1. Further readings between January and March will be used to modify this outline whenever necessary in order to produce a draft of the full text in March. After editing the text to align with peer review comments and collecting additional information to correct gaps and ambiguities in the text, a presentation of the paper's conclusions will occur in early April followed by submission of the completed work in late April.

STS Research Question and Data Collection Methods

The central research question to be answered is whether the measures taken to hinder proliferation of AMR via surveillance, prevention and containment within high income countries (such as the EU) are effective or adaptable for lower income countries. This question's importance is highlighted by the aforementioned rapid rise of antibiotic consumption in many low-middle income countries described by Klein et. al. (2018). It is highly unlikely that the antibiotic consumption rate in these countries will slow down before resistance begins to accumulate; the research will shine some light on what could be done to prevent or reduce an impending health loss.

Policy analysis will be the base method of research, with planning and regulatory documents from government agencies being the starting point of investigation. If plans appear to have failed, audits from regulatory bodies may illuminate whether noncompliance was a determining factor. Details concerning education/awareness campaigns intended to counter AMR in both the consumer and provider domains will be surmised from medical journals or local publications. Infrastructure assessments for planning implementations will be made from urban planning and public works documents (in scientific journals or on agency websites). Research studies on public opinion of efforts to address the AMR crisis will also be assessed for contrast

with official government narratives. Data for policy effectiveness in terms of antibiotic consumption and AMR incidences will be obtained from medical databases and journals wherever possible; a "success" will be defined by a decline in the specific growth rate of whichever variable the policy was designed to address.

Goals for the Undergraduate Thesis

The undergraduate thesis will consist of a technical report detailing a chemical process with specifications for industrial production of lofexidine and a research paper addressing effectiveness and expansion potential of the initiatives taken by the European Union to slow propagation of antimicrobial resistance. The technical report will ideally provide a profitable manufacturing blueprint that could reasonably be adopted by a pharmaceutical company for further development. Supporting the expansion of lofexidine production would alleviate manufacturing shortages when they occur and assist in management of the opioid abuse crisis. The STS research paper will ideally provide a comprehensive analysis of social and technical elements governing the formulation and effective implementation of policies that address the three main areas of AMR risk management (surveillance, prevention, containment). This analysis may be used as a starting point to recommend courses of action for low income countries to assist in reducing the eventual impact of AMR.

References

Adam, B., Beck, U., & Loon, J. van. (2000). *The Risk Society and Beyond: Critical Issues for Social Theory*. London: SAGE.

Akhurst, J. (1999). The use of lofexidine by drug dependency units in the United Kingdom. *European Addiction Research, 5.* 43-49.

Alirol, E., Getaz, L., Stoll, B., Chappuis, F., & Loutan, L. (2011). Urbanisation and infectious diseases in a globalised world. *The Lancet Infectious Diseases*, *11*(2), 131–141. doi:10.1016/s1473-3099(10)70223-1

Bragg, R., van der Westhuizen, W., Lee, J.-Y., Coetsee, E., & Boucher, C. (2014). Bacteriophages as Potential Treatment Option for Antibiotic Resistant Bacteria. In Advances in Experimental Medicine and Biology (pp. 97–110). doi:10.1007/978-81-322-1777-0_7

Bronzwaer, S., Lönnroth, A., & Haigh, R. (2004). The European Community Strategy Against Antimicrobial Resistance. Eurosurveillance, 9(1), 30–34. doi: 10.2807/esm.09.01.00441-en

Bruinsma, N., Hutchinson, J.M., Giamarellou, H., Degener, J., & Stobberingh, E. E. (2003). Influence of population density on antibiotic resistance. Journal of Antimicrobial Chemotherapy, 51(2), 385–390. doi:10.1093/jac/dkg072

Bryce, C. (2019). Lofexidine (Lucemyra) for Treatment of Opioid Withdrawal Symptoms. *Am. Fam. Physician*, *99* (6), 392–394.

Country participation. (2019, October). World Health Organization. Retrieved from: https://www.who.int/glass/country-participation/en/

Crooks, P. A.; Vartak, A. P. (2012). Enantioselective Synthesis of (+) and (–)-2-[1-(2,6-Dichlorophenoxy)-Ethyl]-1,3-Diazacyclopent-2-Ene. US8101779B2.

Disease and laboratory networks. (2012). European Centre for Disease Prevention and Control. Retrieved from: https://www.ecdc.europa.eu/en/about-uswho-we-work/disease-and-laboratory-networks

Erskine, D. (2018). Shortage of lofexidine hydrochloride tablets 200 microgram (BritLofex). *Guy's and St Thomas' NHS Foundation Trust Medicines Information Centre*. Retrieved from: https://www.sps.nhs.uk/articles/shortage-of-lofexidine-hydrochloride-tablets-200-microgram-britoflex/

EU Action on Antimicrobial Resistance. (2017, June). European Commission. Retrieved from: https://ec.europa.eu/health/amr/antimicrobial-resistance_en

FDA Briefing Document - Meeting of Psychopharmacologic Drugs Advisory Committee. (2018, March 27). Food and Drug Administration. Retrieved from: https://www.fda.gov/media/111880/download

Florence, C. S., Zhou, C., Luo, F. & Xu, L. (2016). The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013. Medical Care, 54(10), 901–906.

Fries, R. (2004). Conclusions and Activities of Previous Expert Groups: The Scientific Steering Committee of the EU. Journal of Veterinary Medicine Series B, 51(8–9), 403–407. doi:10.1111/j.1439-0450.2004.00794.x

Global action plan on antimicrobial resistance. (2015). World Health Organization. Retrieved from: https://www.who.int/antimicrobial-resistance/publications/global-action-plan/en/

Huttner, B., & Harbarth, S. (2009). “Antibiotics Are Not Automatic Anymore”—The French National Campaign To Cut Antibiotic Overuse. PLoS Medicine, 6(6), e1000080. doi:10.1371/journal.pmed.1000080

Henriques-Normark, B., & Normark, S. (2014). Bacterial vaccines and antibiotic resistance. *Upsala Journal of Medical Sciences*, *119*(2). doi:10.3109/03009734.2014.903324

Klein, E. Y., Boeckel, T. P. V., Martinez, E. M., Pant, S., Gandra, S., Levin, S. A., … Laxminarayan, R. (2018). Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proceedings of the National Academy of Sciences*, *115*(15). doi:10.1073/pnas.1717295115

Kolodny, A.; Courtwright, D. T.; Hwang, C. S.; Kreiner, P.; Eadie, J. L.; Clark, T. W.; Alexander, G. C. (2015). The Prescription Opioid and Heroin Crisis: A Public Health Approach to an Epidemic of Addiction. *Annu. Rev. Public Health*, *36* (1), 559–574.

Lopatkin, A. J., Meredith, H. R., Srimani, J. K., Pfeiffer, C., Durrett, R., & You, L. (2017). Persistence and reversal of plasmid-mediated antibiotic resistance. *Nature Communications*, *8*(1). doi:10.1038/s41467-017-01532-1

Maron, D., Smith, T. J., & Nachman, K. E. (2013). Restrictions on antimicrobial use in food animal production: an international regulatory and economic survey. Globalization and Health, 9(1), 48. doi:10.1186/1744-8603-9-48

Nicolas, I., Bordeau, V., Bondon, A., Baudy-Floc’H, M., & Felden, B. (2019). Novel antibiotics effective against gram-positive and-negative multi-resistant bacteria with limited resistance. *PLOS Biology*, *17*(7). doi:10.1371/journal.pbio.3000337

O'Neill, J. (2016, May). Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. Retrieved from: https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

Ormrod, J. S. (2013). Beyond World Risk Society? A Critique of Ulrich Beck's World Risk Society Thesis as a Framework for Understanding Risk Associated with Human Activity in Outer Space. Environment and Planning D: Society and Space, 31(4), 727–744. doi:10.1068/d16511

Person, B., Sy, F., Holton, K., Govert, B., Liang, A., … Garza, B. (2004). Fear and Stigma: The Epidemic within the SARS Outbreak. Emerging Infectious Diseases, 10(2), 358–363. doi:10.3201/eid1002.030750

Rehman, S. U.; Maqsood, M. H.; Bajwa, H.; Din, A. T. U.; Malik, M. N. (2019). Clinical Efficacy and Safety Profile of Lofexidine Hydrochloride in Treating Opioid Withdrawal Symptoms: A Review of Literature. *Cureus*, *11*(6).

Rudd, R. A., Aleshire, N., Zibbell, J. E., Gladden, R.M. (2016, January). Increases in Drug and Opioid Overdose Deaths — United States, 2000–2014. Morbidity and Mortality Weekly Report, 64(50), 1378-82.

Scholl, L., Seth, P., Kariisa, M., Wilson, N., & Baldwin, G. (2018). Drug and Opioid-Involved Overdose Deaths — United States, 2013–2017. MMWR. Morbidity and Mortality Weekly Report, 67(5152). doi:10.15585/mmwr.mm675152e1

Solorio, J. (2018). Lucemyra: An Underappreciated Opportunity For Valeant. *Seeking Alpha.* Retrieved from: https://seekingalpha.com/article/4186698-lucemyra-underappreciated-opportunity-valeant

Turton, R. (2018). *Analysis, Synthesis, and Design of Chemical Processes, Fifth Edition*. Boston: Prentice Hall.

Van Boeckel, T. P., Brower, C., Gilbert, M., Grenfell, B. T., Levin, S. A., Robinson, T. P., … Laxminarayan, R. (2015). Global trends in antimicrobial use in food animals. Proceedings of the National Academy of Sciences, 112(18), 5649–5654. doi:10.1073/pnas.1503141112

Vartak, A. P. (2014). The Preclinical Discovery of Lofexidine for the Treatment of Opiate Addiction: Expert Opinion on Drug Discovery. *Expert Opin. Drug Discov. 9* (11), 1371–1377.

Wakeman, S. (2018, August). Lofexidine: Another option for withdrawal from opioids, but is it better? Retrieved from: https://www.health.harvard.edu/blog/lofexidine-another-option-for-withdrawal-from-opioids-but-is-it-better-2018060614515

Wimmer, J., & Quandt, T. (2006). LIVING IN THE RISK SOCIETY. Journalism Studies, 7(2), 336–347. doi:10.1080/14616700600645461