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NOSCAPINE

A SAFE COUGH SUPPRESSANT WITH NEWLY DISCOVERED EFFECTS IN TREATING CANCER AND STROKE

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PC-REF
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1.0 SUMMARY

Noscapine is a very safe cough suppressant (antitussive) which has been in use for many decades. In recent years, noscapine's anti-cancer effect has been demonstrated when taken at doses higher than those used for cough suppression. It is currently in off-label use by a number of physicians in treatment of cancers of the breast, lung, prostate, ovaries and brain, and lymphomas, to name but a few. It is being clinically studied in non-Hodgkin's lymphoma and chronic lymphocytic leukemia (CLL).

Noscapine, a non-addictive derivative of opium, has also demonstrated outstanding clinical effectiveness in reducing death rates from strokes. Its long safety record, widespread availability and ease of administration make it an ideal candidate for fighting several life-threatening conditions.

2.0 HISTORY

In 1817, Pierre-Jean Robiquet, a famous French pharmacist and professor at the Paris Ecole de Pharmacie, fellow of the Academie Royale des Sciences, isolated two natural compounds from opium: codeine and noscapine.[1] Noscapine, formerly known as narcotine, anarcotine or gnoscopine, was classified as an alkaloid. It forms between four and twelve percent of the opium seed.

In the late nineteenth century, opium (*Papaver somniferum*) was known as an anti-malarial medicine. It was mainly produced in India, which was at that time part of the British Empire, and was considered the third pillar of British India's economy. The opium trade was not without controversy, however. This finally prompted the establishment of a Royal Commission on Opium. During the 1893-95 Royal Commission, its medical expert, Sir Robert Williams, concluded that noscapine was responsible for opium's ability to prevent and treat malaria. This was in contrast to the opinion of renowned chemists, who by 1874 had classified it as an insignificant substance possessing minimal or no therapeutic value.[2]

Noscapine's application as an anti-malarial was revived in 1895 at the suggestion of Sir Robert Williams. It remained in use for many years, until a comprehensive study published in 1930 discredited its use for this purpose.[3]

The earliest pharmacological investigations of noscapine attempted to define its analgesic (pain-relieving) properties. It was found that the alkaloid on its own has a very slight analgesic effect.[4] However, when taken with morphine, it acts synergistically to potentiate morphine's sedative effects[4,5] by as much as threefold.[6] Furthermore, noscapine did not cause constipation, unlike the other opium alkaloids such as morphine, codeine, and papaverine.[7]

2.1 COUGH-SUPPRESSING EFFECTS DISCOVERED

Noscapine's antitussive effect was first suggested in 1930,[Error! Bookmark not defined.] and was described more comprehensively in 1954.[8] Studies over the course of the next few years confirmed its general antitussive effect, and specifically the relief it provided to patients suffering from bronchial asthma.[9, 10, 11, 12, 13, 14] A review of the evidence available, as well as extensive further testing, prompted a recommendation in 1959 that noscapine replace codeine as an antitussive.[15]

Since the 1960s, noscapine has been widely used as an antitussive medication throughout Europe, Japan, North and South America, and South Africa. It is listed in the pharmacopeias of many countries including those of Europe, Japan and the United States. It has been administered orally in tablets, lozenges or syrup, and rectally in suppository form.

2.2 ANTI-CANCER EFFECTS DISCOVERED

In 1958, cell culture studies performed for the United States National Cancer Institute found noscapine to possess significant cytotoxic properties.[16] This was similar to findings that had also been reported in 1954.[17] Perhaps due to the fact that it was no longer patentable, no further studies were carried out to determine its effect on treating cancer.

2.3 ANTI-CANCER EFFECTS REDISCOVERED

Noscapine's anti-cancer effect was rediscovered in 1997 by Keqiang Ye, a graduate student at Emory University School of Medicine in Atlanta, USA. Working under the direction of Dr Harish Joshi, professor of cell biology, Ye embarked on an intensive search for compounds which could act as anti-microtubule drugs.

Microtubules are structures involved in cell division. Anti-microtubule drugs disturb the assembly of the microtubules, thus preventing cell division. In normal cell growth, microtubules are formed when a cell starts to divide. Once the cell stops dividing, the microtubules are either broken down or destroyed. Anti-microtubule drugs stop the microtubules from breaking down, thus causing cancer cells to become so clogged with microtubules that they cannot further grow and divide. One of the promising anti-microtubule compounds which Ye came across was noscapine, a common cough suppressant.

The initial study on noscapine by the scientists at Emory University led to some very promising findings. Treating animals which had been transplanted with human breast cancer tumors, they were able to reduce tumor volume by 80% within three weeks. Most importantly, this was done without any visible toxicity to the animals' vital organs. The authors concluded that noscapine reduces tumor size quite dramatically, with no obvious weight loss nor any detected tissue toxicity after noscapine treatment.[18] Conveniently, noscapine's effectiveness could be achieved through oral administration.

The first Emory University noscapine study was published in February 1998 in the *Proceedings of the National Academy of Sciences* in the USA. A subsequent paper published in July 2000 confirmed noscapine's effects against murine lymphoma. In the words of the authors of the study:

> It is noteworthy that noscapine showed little or no toxicity to kidney, liver, heart, bone marrow, spleen, or small intestine at tumor-suppressive doses. Furthermore, oral noscapine did not inhibit primary immune responses, which are critically dependent upon proliferation of lymphoid cells. Thus, our results indicate that noscapine has the potential to be an effective chemotherapeutic agent for the treatment of human cancer.[19]

Further studies were carried out at Emory University to test the effectiveness of noscapine against additional cancers. Among other types, these have

included ovarian cancer,[20] malignant melanoma,[21] bladder cancer,[18] and glioblastoma,[22] all studies having demonstrated very significant results with minimal toxicity.

Dr Joshi and his team have carried out extensive tests in order to try and determine the exact mechanism by which noscapine stops the division of cancer cells. Details of their studies have been published in various medical journals during the past few years.[20,23,24]

Researchers at other institutions have also been studying the anti-cancer effects of noscapine. These include University of Minnesota, USA, and University of Delhi, India. Dr Sundaram Ramakrishnan and his team at University of Minnesota have been studying the effects of noscapine on cancer since 1999.

Dr Ramakrishnan's experiments have demonstrated effectiveness against Taxol-resistant ovarian cancer.[25,26] Models of cervical cancer have also been evaluated,[27] and a paper detailing his team's successful results is pending publication. Dr Ramakrishnan is also exploring the possibility of cancers' eventually developing MDR (mediated drug resistance) to noscapine therapy and ways to avoid this.

2.4 Developing Synthetic Derivatives of Noscapine

Since noscapine has been on the market for many years, the compound itself cannot be patented. Nevertheless, recognizing the potential market for noscapine in treatment of cancer, a use patent was filed by the discoverers in August 1997 on the effect of noscapine against cancer.[28] After several modifications, the patent was finally granted in 2002, and assigned to Emory University.[29]

As noted in the Emory Report,[30] Emory University officials soon realized that they were unlikely to find commercial sponsorship to further develop noscapine:

> The University has submitted a patent on noscapine, but because the drug is already used in cough medicine, the patent only covers its use as an anti-cancer drug. Any company investing heavily in clinical trials [takes] a gamble [on] its ability to recoup capital, since it would not retain sole rights to the drug. This uncertainty has scared off larger companies that usually manufacture synthetic drugs, but Emory officials remain cautiously optimistic.
>
> "The best thing [noscapine] has going for it is that it's been used by people for a very long time, so we know that it's relatively safe—and that's a very big step," said Dennis Liotta, vice president for research. Emory also is looking to devebp additional noscapine analogs—[similar compounds with] synthesized changes to the drug's structure, Liotta said. These slight changes might [make the drug]

even more effective in stopping cancer, and since they would be man-made, the new compounds could be patented.

Subsequent to this, Emory researchers, in collaboration with scientists at University of Delhi, India, worked on somehow modifying noscapine in order that they could patent a derivative whilst maintaining or improving its anti-cancer effect. They succeeded in doing so, and in January 2002 they applied for a patent covering the modified substances. The patent was granted in January 2004.[31] Details of their results were published in 2003, on what they termed "Brominated Derivatives of Noscapine."[32] On June 15, 2004, Emory University finally licensed the rights to commercially develop noscapine and its modified compounds to Cougar Biotechnology in California, USA.[33]

2.5 CLINICAL TRIALS IN CANCER

Following the publicizing of noscapine's anti-cancer effect, many patients suffering from various types of cancer began to use noscapine on their own accord, or at the suggestion of their physicians. Following several anecdotal reports of patients who had failed multiple standard chemotherapy agents and had subsequently responded to noscapine, the Walter Payton Cancer Fund of the Norris Cancer Center, University of Southern California, decided to sponsor a human trial. This Phase I/II trial is targeted at patients suffering from non-Hodgkin's lymphoma or chronic lymphocytic leukemia. It is aimed at clarifying the safe and effective doses of noscapine. The doses used in the trial range from 1,000 to 3,000 mg per day.

In December 2005, positive interim results were presented at the annual meeting of the American Society of Hematology in Atlanta, Georgia.

Much researcher focus is presently concentrated on the new patented synthetic derivatives of noscapine. These new compounds with high commercial potential are making their way from laboratory synthesis through animal testing, and will reach clinical testing within a few years.

2.5.1 Applications in Prostate Cancer

Dr. Israel Barken, Founder and Medical Director of the Prostate Cancer Research and Educational Foundation (PC-REF) in San Diego, California, has used noscapine for treating prostate cancer with patients residing outside the U.S. In the U.S., patients were treated by special permission based on compassionate use clearance. Encouraged by his observations, PC-REF funded a pre-clinical study to confirm noscapine's effectiveness and mode of action in treating prostate cancer.

On Feb. 15th, 2007, Dr. Barken made a presentation at the 17th International Prostate Cancer Update conference in Vail, Colorado. He presented the result of research demonstrating the effect of noscapine on aggressive human prostate cancer implanted in mice.

The results of the study showed:

1. Significant inhibition of the growth of the primary tumor in the treated versus the untreated group.
2. Significantly less metastatic disease in the treated group compared to the untreated group.

Dr. Barken is now moving to facilitate clinical trials with noscapine in patients suffering from prostate cancer. He has also pioneered a web-based patient tracking graph system, (www.pcref.org) which allows data to be collected with ease. This will enable global participation of patients in any trial.

PCREF strongly urges patients who obtain noscapine outside of formal trials to involve their treating physician, and to register their clinical data and medical history on the PCREF web based patient tracking graph system (www.pcref.org). Patients will benefit greatly from having their complete medical history put on a single page, and presented in a colored graph. PCREF will use the collected data to expand the knowledge and understanding of the activity of noscapine in prostate cancer.

2.6 Clinical Trial in Stroke Victims

Bradykinin is a protein produced in the blood in response to injury. Bradykinin activates several mechanisms that are responsible for the early manifestations of inflammation, including arteriolar dilatation, increased vascular permeability, and edema formation. Bradykinin is known to be responsible for much of the brain damage suffered by stroke victims, and several studies have proposed methods of inhibition of bradykinin as potential therapy for the complications of stroke,[34] which is the third leading cause of death in developed countries.

A group of Iranian researchers who were aware of noscapine's effect in suppression of bradykinin, launched a controlled clinical trial of noscapine in victims of stroke. The results of the trial were published in 2003. Using a low dose of noscapine equivalent to that used to suppress coughing, remarkable results were achieved. The noscapine-treated group experienced a 20% mortality rate, as opposed to 80% in the untreated group.[35]

The researchers in this study have attributed noscapine's effectiveness in treating victims of stroke to its antagonism of bradykinin.

3.0 Uses

As of the time of writing, the only formally approved application for noscapine is as a cough suppressant. Usual doses used for cough suppression vary from 45 to 200 mg per day, usually in three divided doses.

Off-label use of noscapine is being made by a number of physicians in treating cancers of the breast, lung, prostate, and ovaries. Clinical trials have

yet to be performed to determine optimal dosages. Dosages currently in use for cancer range between 1,000 to 2,250 mg per day, usually in three divided doses.

Some physicians are using noscapine for its pain-relief effects by combining it with lower-than-usual doses of morphine. The author is presently unaware of any physicians using noscapine for treatment of stroke. This does, however, remain a safe and effective potential application.

4.0 Mode of Ingestion

Noscapine can be given orally in tablets, lozenges, capsules, and syrup, and rectally in suppositories. It has also been tested in intravenous form in humans; however, since oral absorption is found to be satisfactory[36], being additionally safer and far less expensive than intravenous forms, it remains the route of choice. Due to its low molecular weight, Noscapine can be administered trans-dermally in cream form, provided it is combined with an effective penetrant.

5.0 Pharmacokinetics

The common form of noscapine which is used in cough suppression is noscapine hydrochloride (Hcl). Noscapine Hcl has a half-life of 4.5 hours in the body.[37] However, a study performed at the Royal Danish School of Pharmacy in Copenhagen has demonstrated that consumption of noscapine base produces significantly higher bioavailability than that of noscapine hydrochloride (Hcl).[38] It may therefore be possible to achieve more successful results with lower doses of noscapine base than with higher doses of noscapine Hcl.

6.0 Safety and Side Effects

The side effects which have been observed with very high doses of noscapine Hcl have generally been limited to nausea and abdominal discomfort in a small percentage of patients. Extensive toxicology studies carried out in both animals[39] and humans[3,43] have confirmed its extremely low toxicity,[45] with little or no effect on vital organs and blood parameters, and with negligible side effects.[40]

In 1961, a toxicity study on terminally ill cancer patients, many with only days left to live, was carried out by the renowned Dr. Louis Lasagna at Johns Hopkins University. It was found that at daily doses of up to 3,000 mg, 80% of patients experienced no side effects.[41] The other 20% experienced mild sedation and abdominal discomfort. However, this study had no control group and therefore it could not be determined whether the side effects experienced by the minority of patients were due to noscapine or to their terminal illnesses.

Subsequent protocols for animal-based studies on the anti-cancer effect of noscapine (described below) determined what could be considered a “safe” dose according to the results of Dr. Lasagna’s study.

Precaution is required before administering noscapine to patients during pregnancy. In 1991, the UK Committee on Safety of Medicines recommended that noscapine should be contraindicated in women of childbearing potential because of potential genotoxicity.[42] This decision was criticized, however, because it was based solely on the results of in vitro (laboratory) work.[43] Indeed, subsequent animal studies have shown that such hazards were not found with recommended therapeutic doses of noscapine, requiring megadoses equivalent to 28,000 mg for a bodyweight of 70 kg before observing such effect.[44] An in vitro study performed in 1991 by Smithkline Beecham Pharmaceuticals, UK, also concluded that noscapine does not pose a significant potential hazard for humans.[45] The American Academy of Pediatrics considers that noscapine is usually compatible with breast-feeding.[46]

7.0 Mechanisms of Action

To date, several mechanisms of action have been discovered for noscapine.

In the suppression of cough, it is known that noscapine is centrally acting. The only evidence which currently exists points to noscapine's inhibition of bradykinin as the mode by which it functions.

Noscapine's anti-cancer effect has been primarily attributed to its microtubule-interfering effect. Recently, noscapine has been found to have anti-angiogenic properties (preventing the formation of new blood vessels).[51]

Noscapine's effect in treating strokes has been attributed to its bradykinin suppressive effect.

Mechanisms of action in other conditions have yet to be researched and determined.

8.0 Pathways Affected

Noscapine has been shown to affect the following pathways:

8.1 Bradykinin Inhibition

Noscapine has been shown to antagonize bradykinin receptors.[47] Bradykinin is a pro-inflammatory molecule which is responsible for cough. Suppression of bradykinin production has also been suggested as noscapine's mode of action in successfully suppressing cough induced by angiotensin-converting enzyme inhibitors.[48]

8.2 HIF-1alpha Inhibition

Noscapine has been shown to inhibit HIF-1alpha.[49] HIF-1alpha is the main transcription factor activated by hypoxia. Since many cancer cells are

hypoxic, they generate HIF-1alpha production. This in turn leads to stimulation of new blood vessel formation (angiogenesis).

8.3 VEGF INHIBITION

HIF-1alpha acts as a transcription factor for production of vascular endothelial growth factor (VEGF), a potent promoter of angiogenesis. Noscapine, through its inhibition of HIF-1alpha, has been shown to inhibit production of VEGF.[49]

9.0 DISCUSSION

Noscapine's traditional use is for the relief of cough. Both historical and recent research has demonstrated its additional beneficial properties. These include: dramatically increasing the pain-relieving effects of morphine; treatment of strokes; treatment of polycystic ovary syndrome;[50] anti-viral and anti-herpes activity;[56] and in the therapy of cancer.

According to the late Dr. Jonathan L. Hartwell (one of the founders of the US National Cancer Institute), opium has been used for millennia in traditional folk medicine as an anti-cancer agent.[51] Repeated experiments with opium's most known narcotic constituents have failed to demonstrate anti-cancer activity. On the contrary, many studies have found them to be tumor-promoting. The new discovery of the effects of noscapine, the second most abundant alkaloid in opium, may finally solve the mystery behind opium's traditional reputation as an anti-cancer agent.

Whilst the primary investigators at Emory have proposed that noscapine's anti-cancer effect is mediated via arresting microtubules and induction of apoptosis (cell death), an additional mechanism may exist.

Noscapine has been demonstrated to be an effective bradykinin antagonist, and this in fact has been proposed by some authors to be its method of action as a cough suppressant.[52] This finding, too, bears great significance for treating cancer. Since bradykinin is known to be a growth factor for many cancers, researchers have looked for different ways of inhibiting its release of bradykinin.[53] Bradykinin-inhibiting agents have shown a remarkable effect in inhibiting proliferation of cancer cells, far surpassing that of the powerful chemotherapy drug Cisplatin.[54] They have been proposed as therapy for lung cancers (SCLC & NSCLC), as well as prostate cancer.[55]

A newly discovered mode of action of noscapine is its anti-angiogenic activity. This has potential application not only in the treatment of cancer, but also in the treatment of several inflammatory conditions where anti-angiogenic agents have demonstrated effectiveness.

Consideration should be made of the possibility of synergistic effects between the known multiple mechanisms of action of noscapine. Furthermore, it is possible that additional mechanisms of action may be uncovered by future research.

10.0 AVAILABILITY

Noscapine is currently available in several forms as well as dosages, in the following countries:

Argentina (Rx)	**Italy (OTC)**
Australia (OTC)	**Japan (OTC)**
Austria (Rx)	**Korea (OTC)**
Belgium (OTC)	**Netherlands (OTC)**
Canada (OTC)	**New Zealand (OTC)**
Chile (OTC)	**Norway (OTC)**
China (OTC)	**South Africa (OTC)**
Denmark (OTC)	**Spain (Rx)**
Finland (OTC)	**Sweden (OTC)**
Germany (Rx)	**Switzerland (OTC)**
Ireland (Rx)	**USA (OTC) ***
Israel (Rx)	

Rx = prescription required OTC = over the counter * = not widely distributed

11.0 CONCLUSION

Noscapine, a naturally occurring compound, is produced from the opium plant. It is also found in minute quantities in tomatoes and cabbage leaves.[56] Noscapine has been in clinical use for over fifty years for the treatment of cough. It has a long-established safety record.

Noscapine's newly discovered and as yet unofficially approved clinical applications include the treatment of cancer, stroke and polycystic ovary syndrome.

The low toxicity and high bioavailability of orally administered noscapine is quite unparalleled in cytotoxic therapies. Coupled with its easy availability, low cost, and supporting preclinical and clinical research and experience, noscapine proves to be a suitable experimental therapy for both solid and non-solid malignancies. Noscapine's safety and potential of reducing the death rate from stroke by 75% should qualify it for off-label use in such circumstances.

Noscapine's unique multiple applications, in conjunction with its well-established safety record, should encourage further in-depth research and development of its use in treating and reversing a variety of serious medical conditions. In the meantime, it is freely available, and can be used at the discretion of a physician in appropriate circumstances.

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The MedInsight Research Institute is a US-based 501(c)3 non-profit public organization co-founded by Moshe Rogosnitzky of Israel and Dr. David Youlton of the UK.

MedInsight's mission is to alleviate the suffering of those afflicted by life-threatening or chronic medical conditions. It does so by providing comprehensive scientific reviews of data regarding commercially-unsponsored medications, long-lost therapies, and specialized tests that enable the personalization of medical treatment.

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About Prostate Cancer Research and Educational Foundation (PCREF)

PC-REF, a 501(c)(3) non-profit public foundation based in San Diego, California. It was founded by Dr Israel Barken in 1997. PC-REF focuses on patient empowerment, and financially supporting innovative prostate cancer research projects. Their focus is on research ideas that can benefit today's patients.

To Support Clinical Research of Noscapine in patients suffering from prostate cancer please Visit

www.pcref.org

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