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ENVIRONMENTAL SCAN 255

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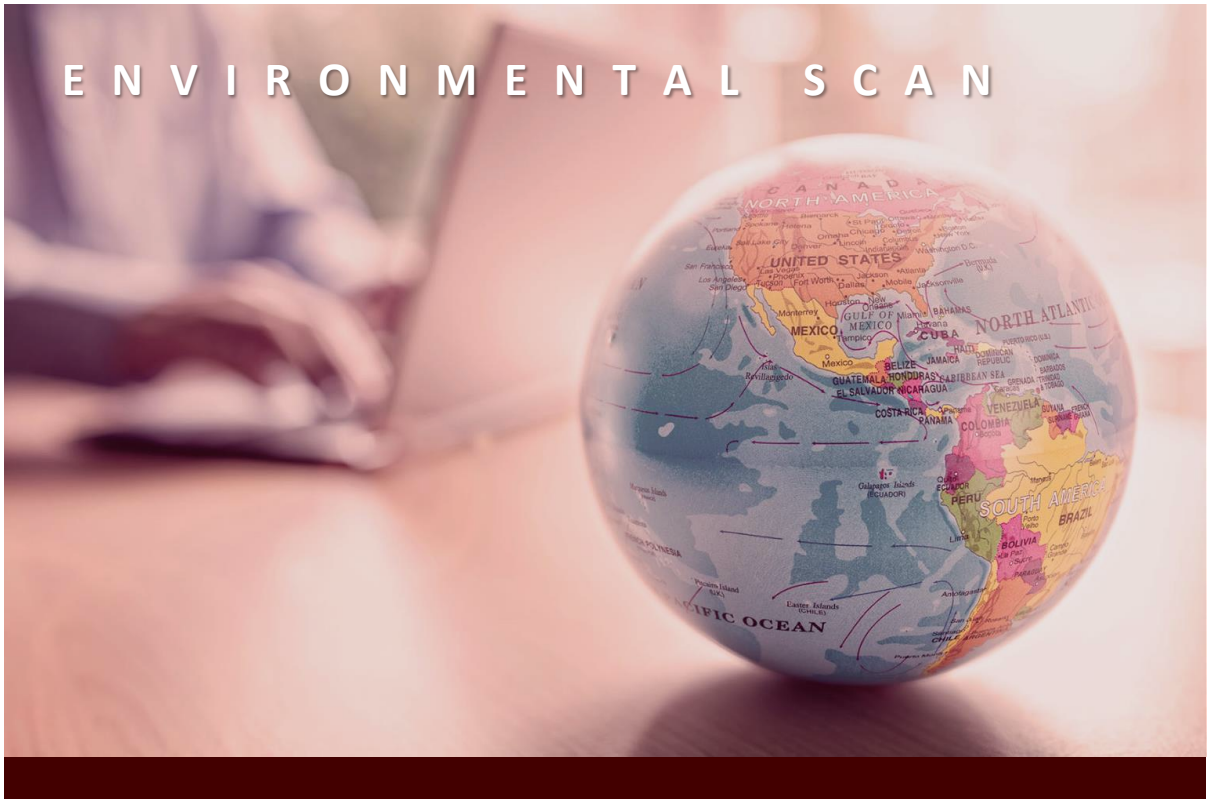

Silica exposure-related disease

Current and emerging treatment options

An Environmental Scan of treatment options for occupationally-acquired silica-related disease

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A joint initiative of WorkSafe VICTORIA and MONASH University

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Abbreviations

Abbreviation	Term
AZT	Azithromycin
CI	Confidence intervals
CT	Computed tomography
COPD	Chronic obstructive pulmonary disease
ECMO	Extracorporeal membrane oxygenation
IPF	Idiopathic pulmonary fibrosis
ISCRR	Institute for Safety, Compensation and Recovery Research
PAP	Pulmonary alveolar proteinosis
PMF	Progressive massive fibrosis
RCT	Randomised controlled trial
RCS	Respirable crystalline silica
TNFα	Tumour necrosis factor-α
US	United States

EXECUTIVE SUMMARY

Background

Inhalation of respirable crystalline silica dust (RCS) is an occupational hazard for workers in stonemasonry, construction, mining and other industries; and may lead to debilitating and often fatal lung diseases such as silicosis. In particular, there has been a recent surge in silicosis cases amongst workers in the artificial stone benchtop industry. As a result, WorkSafe Victoria has received an increase in the number of compensation claims for occupationally-acquired silicosis.

Purpose

The key research questions for this project were:

1. What current, emerging and potential treatment options are available in Australia and internationally for patients with occupationally-acquired crystalline silica diseases?
2. What current, emerging and potential treatment options have demonstrated improvements in outcomes and wellbeing for patients with occupationally-acquired crystalline silica diseases?
3. Which identified potential treatment options could/should be made accessible to claims by workers with occupationally-acquired crystalline silica diseases?

Approach

This Environmental Scan comprised two approaches:

1. Worldwide desktop scan: publicly available online resources included peer-reviewed literature published between January 2010 and January 2020, national and international standards and guidelines, government and industry reports.
2. Key informant interviews: 11 interviews were undertaken with clinical experts, researchers and other stakeholders working in the area of silica-related diseases.

Key findings

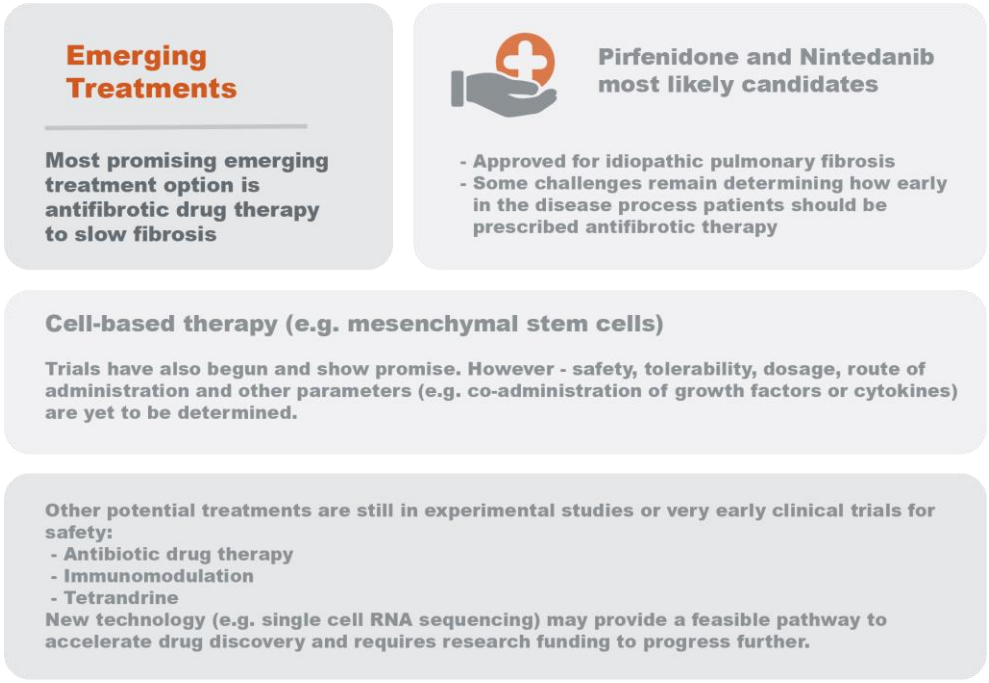
Diagnosis and prognosis: Although early detection is enabled by routine health screening of workers at risk of silica exposure, the extent and rate of disease progression, if detected early, is uncertain. A positive diagnosis may have considerable impact, not only on workers' physical health, but also on their psychological wellbeing and financial futures.

Early management and administrative actions: Key informants agreed that the first steps following a positive diagnosis are to remove the worker from risk of further exposure; and address the challenges related to compensation and medico-legal issues.

Early intervention and support: Smoking cessation; maximising cardiovascular and respiratory health; and providing psychosocial support were recommended as essential for all silicosis patients. Whole lung lavage to reduce the silica load in patients' lungs may be considered, particularly for early stage disease; however, the long-term benefits for silicosis patients are unknown.

Mid-stage treatment and symptom management: There are no current treatment options that effectively halt disease progression or reverse lung damage. Key informants recommended individualised management of symptoms and complications at the discretion of the treating clinician. There was no evidence to support the use of corticosteroids; and while conventional pulmonary rehabilitation programs were beneficial for other lung diseases, they may require modification to successfully engage younger cohorts of silicosis patients.

Late-stage treatment: The only available option for late-stage silicosis is lung transplant. Key informants cautioned against waiting too long before referring for transplant as the surgery becomes more difficult in severe cases. Lung transplant is also limited by the availability of donor organs and the requirement that patients have quit smoking.



Insights and implications

Prevention, early detection and accurate diagnosis are critical for all workers at risk of silica exposure, irrespective of the industry. Removing workers from further exposure is the essential first step after diagnosis and this has major psychological and financial implications for workers' wellbeing. Therefore, understanding the disease course after workers are removed from exposure is critical to determining their treatment options and relies on regular monitoring.

While the current array of silicosis treatment options is limited primarily to managing symptoms and complications, clinicians are poised to take advantage of various advances in research knowledge and technologies. Ultimately, their success will depend on the availability of adequate funding to expedite appropriate investigation in this area.

INTRODUCTION

Crystalline silica is found naturally in sand, stone, quartz and granite; and in the manufacture of composite materials such as concrete, bricks, tiles and engineered (artificial) stone benchtops for kitchens and bathrooms. Cutting, grinding, polishing or drilling materials containing silica releases small particles that are inhaled deep into the lungs. Exposure to respirable crystalline silica (RCS) is associated with silicosis, a debilitating and deadly lung disease that is characterised by lung inflammation, swelling, scarring and breathing difficulties. The health outcomes of silicosis vary according to the level and duration of exposure (Table 1).

Table 1. Types of silicosis associated with silica exposure and clinical outcomes

Type of silicosis	Duration of exposure	RCS concentration exposure	Clinical outcomes
Acute silicosis	< 5 years	High concentration	• Rapidly progressive dyspnoea • Cough • Weight loss • Progression to respiratory failure
Accelerated silicosis	5-10 years after initial exposure	High concentration	• Rapidly progressive dyspnoea • Cough • Weight loss • Progression to respiratory failure
Chronic silicosis	10+ years of exposure	Low concentration	Simple silicosis • Asymptomatic with upper lobe nodules <1cm in size • Chronic cough or exertion dyspnoea • Can progress to complicated silicosis Complicated silicosis (progressive massive fibrosis) • Nodules conglomerate into masses >1cm in size • Chronic cough • Exertional dyspnoea • Weight loss • Progression to respiratory failure

Source: Ennis & Yates (2019)[1]

Although the pathogenesis is still unclear, it is believed that inhaled RCS particles are phagocytosed by the alveolar macrophages, disrupting cell membranes and killing macrophages. Inflammation and injury to the alveolar epithelial cells leads to abnormal healing and formation of scar tissue (fibrosis). Over time, this results in decreasing lung capacity, restricted respiratory function and stiffening of the lungs. Patients with silicosis may require support to help their breathing.[2]

RCS has been a known occupational hazard for workers in construction, mining, stonemasonry and various manufacturing industries since the 1930s; and the more recent development of artificial stone benchtops has seen a surge in silicosis cases in Australia and internationally.[3] The substantial increased incidence of silicosis has been attributed to two main factors: 1) the housing boom has led to rapid expansion of the artificial stone industry for kitchen and bathroom benchtops, as artificial

stone is relatively inexpensive;[4] and 2) artificial stone has much higher levels of silica (>90%) compared with natural sandstone (67%) or granite (25-40%).[5]

In Australia, the first cases appeared in 2016; and a case series was published in 2018.[6] In this case series, Hoy et al. reported that artificial stone workers were dry cutting the stone and did not use precautions against dust inhalation. Moreover, compared with historical silicosis cases, the latency for disease development was significantly abbreviated, the lung function declined more rapidly and cases were identified at a more advanced stage of the disease.

Current data indicate that approximately 20 percent of Australian stonemasons[a] exposed to RCS are at risk of developing a lung condition.[7]

WorkSafe Victoria commissioned ISCRR to identify current, emerging and potential treatment options for patients with occupationally-acquired crystalline silica diseases.

[a] https://www.9news.com.au/health/lung-disease-present-in-20-per-cent-of-queensland-stonemasons/778abf2c-f177-4334-ab9a-e144fd84b232

OBJECTIVES

The objective of this project was to identify current and emerging treatment options for occupationally-acquired diseases related to silica exposure.

Research questions

1. What current, emerging and potential treatment options are available in Australia and internationally for patients with occupationally-acquired crystalline silica diseases?
2. What current, emerging and potential treatment options have demonstrated improvements in outcomes and wellbeing for patients with occupationally-acquired crystalline silica diseases?
3. Which identified potential treatment options could/should be made accessible to claims by workers with occupationally-acquired crystalline silica diseases?

METHODS

This Environmental Scan involved two approaches:

1. Worldwide desktop scan (online): A scope and review of online resources, including peer-reviewed publications, national and international standards and guidelines, government and industry reports
2. Key informant interviews: Insights, experiences and current clinical practices from experts working in the area of silica-related diseases.

Worldwide desktop scan

A comprehensive search of databases (Medline, Embase, Cochrane, Scopus) was undertaken to identify relevant research published from January 2010 to January 2020. The search strategy involved a combination of the following terms: 'silica' OR 'silicosis' OR 'pulmonary fibrosis'; and 'treatment' OR 'intervention'.

The inclusion and exclusion criteria for the desktop scan are listed in Table 2.

Table 2. Inclusion and exclusion criteria for literature searches

	Inclusions	Exclusions
Patient / population	Any workers diagnosed with an interstitial lung disease (e.g. pulmonary fibrosis, pneumoconiosis) that has similar symptoms to silicosis (i.e. respiratory illness and lung fibrosis)	Workers exposed to other hazardous materials that develop illnesses with a different pathogenesis
Intervention / indicator	Any intervention or services for treating or managing the symptoms related to silica exposure	None
Comparison / control	Standard care or no comparator	None
Outcomes	Improvement in respiratory function, quality of life; or any outcomes that demonstrate slowed disease progression	None
Setting	Any setting	None
Study design	Any controlled or uncontrolled study that investigates treatment options for silica-related diseases	Opinions, letters, editorials or articles that do not address treatment options
Publication details	Peer-reviewed publications; grey literature	None
Time period	Articles published between 2010 and January 2020	Articles published before 2010

As it was expected that published evidence may be scarce, a snowballing approach was used to identify relevant material not identified in initial searches. This involved scanning reference lists and following up articles and reports not identified in the initial searches.

Relevant websites (e.g. Lung Foundation, Safe Work Australia) were scanned to identify reports, clinical practice guidelines and workplace safety standards.

Due to time constraints and the expected lack of rigorous clinical studies, no quality assessment was conducted for the studies included in this review.

Key informants

Potential key informants were identified from the published literature and recommendations from members of the working group. Potential interviewees were contacted initially by email, inviting them to participate.

Interviews were recorded and transcribed; and key themes were extracted and reported in a qualitative synthesis. Table 3 lists the 11 key informants who participated in interviews.

Table 3. Key informants who were interviewed for this project

Dr Jane Bourke	Respiratory Pharmacology Group, Monash University, Victoria
Professor Dan Chambers	Respiratory and Sleep Medicine Physician, Queensland
Dr David Deller	Respiratory Physician, Queensland
Professor Tim Driscoll	Professor of Epidemiology and Occupational Medicine at School of Public Health, University of Sydney, New South Wales
Dr Bob Edwards	Respiratory and Sleep Medicine Physician, Queensland
Dr Graeme Edwards	Occupational Physician, Queensland
Dr Ryan Hoy	Senior Research Fellow, Occupational and Environmental Health Sciences, Alfred Hospital, Victoria
Ms Janine Reid	WorkCover Qld, Legal Counsel, Queensland
Professor Malcolm Sims	Professor of Occupational & Environmental Health Sciences, Monash University, Victoria
Professor Gregory Snell	Lung Transplant service, Alfred hospital, Monash University, Victoria
Associate Professor Deborah Yates	Senior Staff Specialist at St Vincent's Hospital, Sydney, Conjoint Associate Professor at UNSW and Co-Chair of the Coal Mine Dust Lung Disease (CMDLD), New South Wales

FINDINGS

Prevention is still considered the best practice for workers exposed to RCS; and current management of silicosis has focussed primarily on administrative actions, such as removing workers from silica exposure and helping them to find work elsewhere. Current treatment options focus on alleviating symptoms and comorbidities as, while several novel potential treatment options are in development, there is limited robust research and no consistently effective therapies that reverse or halt the progression of silicosis.[8]

Silicosis is described as an 'orphan disease' as it is considered relatively rare and, as a result, there is little financial incentive for the pharmaceutical industry to develop or market new medications. Therefore, for the purposes of this project, we have expanded our review to include any health care approaches that address the spectrum of silica-related diseases and similar progressive phenotypes (e.g. idiopathic pulmonary fibrosis); and are characterised by declining lung function, restricted respiration, deterioration of quality of life and poor prognosis. This includes interventions to:

- Ameliorate symptoms associated with poor lung function (e.g. bronchodilators)
- Slow the progression of disease (e.g. antifibrotic drugs)
- Rehabilitate and support patients throughout the disease process (e.g. psychosocial interventions)
- Restore lung function (e.g. transplant).

The findings in this report were based on a combination of the available evidence from published studies; and key informants' perspectives on issues related to diagnosing, treating and managing workers with silica-related conditions. Findings are presented in the following sections:

- Prevention: safety guidelines and standards
- Diagnosis and prognosis: identification of cases and health monitoring
- Early management: administrative actions
- Current interventions:
    - Early intervention and support
    - Mid-stage treatment and symptom management
    - Late-stage treatment
- Emerging treatments: experimental studies and early clinical trials
- Treatments not supported by evidence.

PREVENTION

What's necessary is appropriate prevention and control. Because that will avoid the very vast majority of cases in the first place. … Just important to focus on the fact that prevention is the primary issue. It's a very preventable disease.
Key informant #1

To date, silicosis has been characterised as "untreatable, but preventable";[9] and a key focus has been on protecting workers by reducing worker exposure and managing risks in the workplace using the hierarchy of controls (Table 4).

Table 4. Hierarchy of controls

Level of control	Action
1. Substitution	Source materials with lower silica content
2. Isolation	Designate specific areas for activities that generate silica dust; using automation and/or positioning workers at a distance
3. Engineering	Implement local exhaust ventilation; water suppression (wet cutting); and using tools with dust collection attachments
4. Administrative	Use good housekeeping policies; shift rotations and modified cutting sequences to limit exposure
5. Personal protective equipment	Provide appropriate respiratory equipment (at least P2 efficiency half face respirator); and clothing that does not collect dust

Source: Safe Work Australia (2019)[5]

The current Australian workplace exposure standard for RCS is 0.1mg/m^3 (8 hour/day weighted average).[5] However, Victoria reduced the exposure standard to 0.05mg/m^3 in December 2019; and on 20th February 2020, the NSW government announced that from July 2020 the dust exposure limit would also be reduced to 0.05mg/m^3, two years earlier than initially planned.[b] The Cancer Council have suggested the limit be set at 0.02mg/m^3 to align with international standards.

Engineering and compliance

The danger can be markedly reduced by what is known as 'sheet flow' wet cutting, turning dust into a slurry[10]

Controlled experiments showed that local exhaust ventilation on powered hand tools, combined with sheet-flow-wetting during cutting, significantly reduced exposure to RCS by up to 95 percent; whereas spray wetting on the grinding cup was less effective when combined with local exhaust ventilation.[11]

[b] https://www.brisbanetimes.com.au/business/workplace/nsw-to-ban-dry-cutting-of-stone-products-to-combat-deadly-silicosis-20200220-p542qr.html

In 2018, Queensland banned dry cutting of artificial stone.[4] It was banned in Victoria in August 2019 and the NSW government will ban all dry cutting from July 2020.

However, as remarked by one key informant, the introduction of bans does not guarantee compliance:

> *Just because a code is introduced and there's compliance enforcement, doesn't mean there's compliance. - Key informant #2*

In November 2018, the Queensland government undertook a state-wide audit of 138 engineered stonecutting premises.[7, 10] Workplace Health and Safety Queensland issued 552 compliance notices related to: inappropriate workplace cleaning practices; dry-cutting of engineered stone material; lack of health monitoring for workers; and failure to provide appropriate respiratory protective equipment.

> *There's probably three workshops where, if you spent longer than three years in one of those three workshops, the likelihood that you've got silicosis is more than 70%. - Key informant #3*

Health screening program and register

Since September 2018, Queensland has implemented a health screening program for all workers in the industry.[4] Recently, the UK Government has also been urged to implement a screening program.[12]

In May 2019, WorkSafe Victoria launched a free silica health screening program for past and present stonemasons. The first 12 months has seen over 700 registrations; and 65 per cent have completed the screening process resulting in 78 known positive diagnoses resulting in claims.

In 2019, WorkCover Queensland conducted health screening of 990 stonemasons exposed to RCS and found that 195 had been diagnosed with work-related illnesses: 159 had silicosis (16%); 26 had progressive massive fibrosis (3%); and 10 had other respiratory illnesses (1%).

Currently, the incidence rate of silicosis is not certain as there is no nationwide system for recording cases. However, a National Dust Disease Taskforce has been established to develop a "national approach to the prevention, early identification, control and management of dust diseases in Australia".[13] A key recommendation from the National Dust Disease Taskforce interim report was to establish a *National Dust Disease Registry* to identify new cases through a notification process.[14]

In addition, the NSW Government announced it will introduce a Silicosis Health Register where all silicosis cases have to be listed so the health of exposed workers can be monitored. Safe Work Australia[5] recommended collecting the following minimum dataset:

- Demographic, medical and occupational history
- Records of personal exposure
- Standardised respiratory questionnaire
- Standardised respiratory function tests (e.g. FEV_1, FVC and FEV_1/FVC)[c]
- Chest X-ray full posteroanterior view (baseline and high-risk workers).

[c] FEV_1 = forced expiratory volume (amount of air exhaled in 1 second); FVC = forced vital capacity (total amount of air exhaled forcefully); FEV_1/FVC = proportion of vital capacity exhaled in first second (normal values are ~80%)

In a recent article, Petersen[15] identified seven challenges related to medical surveillance for silica workers in the United States. Many of these challenges may be similar to those faced by the artificial stone benchtop industry in Australia. A summary of the challenges are:

1. Understanding the silica regulations: There is confusion about the standards pertaining to silica workers (these also differ across States in Australia). Petersen reported that managers are uncertain about:
    a. Which employees need medical exams
    b. What information is needed for the exam and which tests to perform
    c. How to interpret results from tests
    d. What is appropriate follow-up after testing
    e. Payments for follow-up exams.
2. Employee refuses exam: Although a medical exam should be offered, employees may refuse to provided medical history or decline the medical exam/tests. In the US, employers may choose to make medical exams a condition of employment.
3. Training of health care professionals: Knowledge of the regulations, potential hazards of silica, understanding and interpreting test results and providing clear medical recommendations about silica-related illness are essential for both the employer and employee.
4. B-reader licensing: In the US, Petersen[15] reported that there was confusion about the need for National Institute for Occupational Safety and Health (NIOSH)-certified B-Readers to review and interpret x-rays.
5. Referral to qualified medical specialists: The US standards require employers to refer employees with identified occupationally-acquired silica conditions to a qualified specialist. However, without guidance and support, locating appropriate specialists may present difficulties for employers.
6. Employee does not authorise release of information to employer: Employees may refuse employers' access to information from medical examinations, such as recommendations on limiting exposure to RCS or referrals to a pulmonary disease specialist.
7. Confidentiality about medical information: In the US, while employers typically receive information on medical exam results and about exposure to hazardous materials in the workplace, the new US standards on silica prevent employers from having access to this information without employee authorisation.

Petersen[15] suggested that, given the complexities of the US Occupational Health and Safety Administration (OSHA) regulations, employers should work with a "compliance partner" (e.g. Safe Work Australia) to guide them through the regulations and employer obligations.

Other preventive approaches

In order to ensure appropriate safety measures are implemented in workplaces, a new licensing scheme has recently been proposed in Victoria, whereby employers who use engineered stone for benchtops will require a licence.[d]

Other preventive approaches include better education about the hazards of working with silica for both employers and workers; and better screening and diagnosis to identify health effects earlier.[4] For example, workers should receive information about the potential health effects of exposure to RCS, including Material Safety Data sheets for all the materials containing silica; instructions about the boundaries and cleaning procedures of work areas; and training in handling materials and protective equipment.

Although the stone benchtop industry is currently in the public eye, there are other industries where silica exposure may put workers at risk. For example, one key informant (#4) raised concerns about carpenters using new composite materials, such as HardiePlank weatherboard, which contains up to 60 percent silica; and suggested workers in other relevant industries should also be monitored to detect early signs of silicosis.

> *This is just the tip of the iceberg because if you look at the James Hardie website, their new partitioning board has got about 60% silica in it. How many carpenters do you see wearing protection when they're cutting that stuff? … unless they have screening medicals they're not found until it's very late. - Key informant #4*

Although there is limited scientific research on silicosis, a recent article emphasised that no further evidence is required before taking action to prevent silicosis in workers exposed to silica.[16]

[d] https://www.miragenews.com/licensing-scheme-to-boost-engineered-stone-safety/

DIAGNOSIS AND PROGNOSIS

The diagnosis has been exponentially worse than the disease. - Key informant #3

Key points

- Early diagnosis is important to prevent cumulative effects of silica exposure; and the current health screening program for stonecutters has identified workers in an early, asymptomatic stage
- Accurate diagnosis is critical to ensure appropriate management of silicosis cases, based on prognosis for the different disease stages
- Workers need a clearer understanding of the uncertainties related to disease progression, as this may impact on management of their physical health, mental health and re-employment opportunities
- Biomarkers are under development to aid accurate diagnosis and staging of the disease
- Monitoring silicosis patients is important to determine the rate of disease progression.

Due to the rarity of silicosis cases, there are many gaps in our knowledge about the pathophysiology, diagnosis and course of the disease. Morbidity and mortality is high in patients with advanced or complicated silicosis; and, currently, there are no treatments that can reverse the loss of function. However, even less is known about the prognosis of the disease if detected at an early stage, such as in asymptomatic patients identified through health screening.

Early diagnosis

Regular health screening of silica-exposed workers is important to ensure signs of silicosis are detected as early as possible. A case-finding/health screening program, which is currently used in Queensland, Victoria and South Australia,[1] proactively identifies silicosis amongst workers in the stonecutting industry.

The health screening program for artificial stone workers was highlighted by key informants as critical to early diagnosis:

> *It is, really, through the development of the health screening program, which started about last May, that's really been key in, actually, identifying a lot more workers with it. - Key informant #5*

Diagnosis of silicosis typically occurs by chest X-rays or computed tomography (CT) scans of workers who have been exposed to silica. CT scans are more sensitive and can detect disease at an earlier asymptomatic stage.[1] A positive diagnosis is determined when there is a history of occupational exposure to silica and a CT scan shows a distinctive pattern of inflammation and scarring in the form of nodules in the lungs.

Typically, silicosis cases described in international peer-reviewed literature have progressed to a moderate-severe stage, where patients experience declining lung function and other symptoms. In contrast, most cases identified through Australia's stoneworkers' screening program have been diagnosed at an early, asymptomatic stage.

> *I think the Queensland cohort is likely to be quite different from other cohorts from around the world just because of the way it's been acquired…. There aren't that many still coming through from screening, so we've probably captured, I'd say definitely by far, the majority of the workers in Queensland. Key informant #6*

Key informants agreed that the prognosis in these early stage cases is unknown; and that "for most there seems to be a reasonably benign course" (Key informant #6) once workers are removed from exposure. However, a proper analysis of the data and longitudinal follow-up of patients are needed to confirm this.

According to one key informant, the screening program has provided a unique dataset of patients with early-stage silicosis; and a rare opportunity to follow the natural history of a disease that is not fully understood. However, no current funding is available to appropriately interrogate the data.

> *We're just flabbergasted at the lack of any, even modest funding. It's literally been zero - zero dollars in research funding for silicosis. … It's information that's vital for determining what is the best course of action for any individual worker, not just in Australia, but around the world. - Key informant #6*

> *We're trying to make decisions about what to do with the worker and naturally there's a lot of unknowns at the moment. … But in many respects, we could've answered those questions, which will now be costing WorkCover or the government or whoever or the worker a lot of money. - Key informant #6*

Accurate diagnosis and prognosis

While early diagnosis is important, accurate diagnosis and prognosis are critical as these may impact substantially not only on workers' physical health, but also on their mental health, employment opportunities and overall wellbeing.

One key informant suggested that cases are still misdiagnosed as sarcoidosis, which causes similar lung changes:

> *Our first lots of coal workers in 2015 …they were diagnosed as sarcoidosis and we had to get them to have lung biopsies and show that they were really coal workers. Some of it is to get the diagnosis right. - Key informant #4*

Although the characteristics of advanced silicosis are recognisable, key informants stated that there is no consensus on the minimum diagnostic criteria for early, mild or moderate stages, particularly if a worker is asymptomatic.

> *There's no clear guidelines of what really constitutes mild or early disease. Diagnostically it's very challenging. - Key informant #3*

As a result, key informants suggested that, without proper guidelines around diagnosis, there is likely to be over-diagnosis in some jurisdictions and under-diagnosis in others; and this may impact on treatment strategies as well as compensation decisions.

If you're going to introduce therapy then probably doing it at an earlier point is going to be much more helpful, but you're not going to want to do that if you don't have some diagnostic certainty as to whether it's actually the disease or it's smoking-related or bong-related, or ice-related, or whatever else they're inhaling into their lungs that they don't want to tell you about. - Key informant #3

We're left with the same predicament. We've got mild radiologic abnormalities with no symptoms and normal lung function. What is the threshold for calling this disease? - Key informant #3

Biomarkers for silicosis

Currently, there are no definitive biomarkers for silicosis. While there are significant differences in levels of several markers in serum (e.g. copper, zinc, selenium, neopterin, heme oxygenase-1, angiotenisin-converting enzyme and Clara cell protein) compared with normal unexposed controls,[17] it is not clear whether they are markers of exposure or biomarkers of disease.

At the moment, the only markers of disease progression we've got are the crude ones called changes to the radiology appearance or changes in their pulmonary function test. We would be better served if we had a biomarker that more readily reflects the disease process rather than the magnitude of the disease process affecting that individual. - Key informant #7

Preliminary studies have shown promising results with single-cell RNA sequencing on lung tissue from patients with idiopathic pulmonary fibrosis (IPF).[18] Results showed a distinct population of cells that promote fibrosis and may provide a target for developing specific drug therapies.

Key informants confirmed this as a promising pathway for future research:

Historically, when we've been looking for biomarkers, any specific biomarker that might have had some early promise hasn't materialised as having the robust functionality that we're looking for. I'm optimistic that the single-cell RNA sequencing is actually going to fit the bill. - Key informant #7

It's now possible to completely describe the normal and abnormal cellular composition of any tissue. … there's several groups around the world, who've taken that approach, to describe what cells look like in pulmonary fibrosis and compare them to normal cells. And that way, you can see all the transcripts that are abnormally expressed and that way you can then target therapy, work out which transcripts are the ones that are driving the disease. - Key informant #6

This approach is currently being investigated for silicosis:

We think we know which cell type we will see that's driving fibrosis and it's probably a macrophage cell type that we've seen before in other diseases. And that points to the drug that's most likely to be most effective. - Key informant #6

New technology

- Recently, a point-of-care test for silicosis has been developed and tested in RCS-exposed rats.[19] The lab on a chip (LOC) immunoassay is highly sensitive to tumour necrosis factor (TNFα), a protein biomarker that contributes to silica-induced lung inflammation and fibrosis. The LOC was able to detect low concentrations of TNFα (16pg/ml) in plasma and the analysis took approximately 30 minutes. While this needs to be tested in a clinical setting, it holds promise as a sensitive, non-invasive and rapid diagnostic test for silicosis.
- New technology developed at Monash University may also have the potential to diagnose lung diseases and monitor treatment outcomes more efficiently. The new X-ray technology allows researchers to view airflow in the lungs in real-time and to see localised areas of dysfunction. While this is still in early stages, it is promising for early diagnosis and non-invasive management of lung disease.[20]

Uncertainties in prognosis

In one key informant's experience (#3), most patients referred through the stonemasons' health screening program were predominantly young males, with no symptoms of respiratory impairment. Although a diagnosis of early stage silicosis was made "on the balance of probabilities" from occupational history and CT scan results, the key informant (#3) stated that, at this point in time, there is no way to know whether the disease would progress once the worker ceased exposure to RCS. Most research has been conducted on patients with symptoms of lung impairment and moderate-severe lung fibrosis. While the prognosis for those patients is poor, there is insufficient evidence on outcomes for patients identified at an early, asymptomatic stage of the disease.

> *Many of my patients that I've been seeing and following who have been diagnosed in 2018 with very early disease and they're no longer exposed to silica haven't progressed. That's 18 months. - Key informant #4*

Consequently, a key informant (#3) suggested that workers need a clearer understanding of the uncertainties around whether their disease is likely to progress once detected early. This is critical to the approach used to address not only their physical health, but also their mental health and wellbeing. Key informants explained the challenge of diagnosis in asymptomatic patients:

> *As soon as someone actually has an established diagnosis, the majority of those actually don't have primary respiratory dysfunction. There are some that's going to appear to rapidly progress and there are those who seem to be quiescent. And we don't yet know who falls into which category and, in particular, why. So, it's the uncertainty. - Key informant #7*

> *We were terrified, understandably, initially because every case that we saw had very advanced disease or progressive massive fibrosis with lung function impairment, even though they were asymptomatic. - Key informant #3*

> *One of the big issues is that everyone keeps telling them that they're going to die, and they're going to die of their disease. But actually, it's the uncertainty of the condition … where we don't even know if it's going to progress. I mean, we've got it so early, or in such a mild case, that there's the possibility that they don't progress. - Key informant #3*

If you make a wrong call early, you remove people from an industry which is all they know and all they can do. We know that the psychological impact is massive, so on the basis of very little information, other than some ground glass stuff on a CT, you've really taken away their livelihood. That really should be avoided, and if we have ways of identifying the disease, with more certainty, then I think we would be much more comfortable making those really difficult decisions.
Key informant #3

Monitoring disease progression

Key informants highlighted the need for monitoring cases over time to address the gaps in knowledge about the disease progression.

At the moment, we're making it up as we go. … At one stage, we're doing four months of reviews. That's probably too frequent. Whether it's six months or eight months or 12-month reviews, we're yet to get a consensus on that. The frequency of monitoring will depend upon the nature of the pathologies that that individual is already manifesting compounded by and influenced by the availability of potential treatments. - Key informant #7

EARLY MANAGEMENT AND ADMINISTRATIVE ACTIONS

It goes without saying, just simply being removed from the exposure is the critical intervention. Probably for many workers that's all that will need to be done.
Key informant #6

Key points

Early management involves:

- Prudent avoidance: remove workers from RCS exposure **[Strong support – expert opinion]**
- Job modification or re-training in an alternative industry
- Compensation may be short-term until they are re-employed; or receive a terminal benefit; and may impact on treatment approaches
- Medico-legal issues arise, particularly where there are conflicting perspectives between workers, lawyers and clinicians.

Once a diagnosis of silicosis has been confirmed, early management and administrative actions follow, including:

- Prudent avoidance: removing workers from the silica environment to avoid further exposure
- Job modification or re-employment: supporting workers in change of employment
- Compensation: workers' compensation and medico-legal issues.

Prudent avoidance

After diagnosis, the strong recommendation by all key informants was to avoid further exposure – termed 'prudent avoidance'. If job modification options are not feasible, the worker most likely will need to leave the industry.

> *The primary thing is to look at job modification and, unfortunately, usually requires them to not return to work in that stone benchtop industry.*
> *Key informant #5*

Based on information from key informants, workers identified with silicosis through the health screening program in Queensland were at various stages of disease and many were under 30 years old:

> *We've got a number of very young workers between 20 and 30 with different personal circumstances too. Sometimes that's been a bit challenging in terms of managing what the next steps are. - Key informant #2*

While avoiding further exposure seems simple and indisputable, this may have a considerable impact on workers whose earning potential has suddenly disappeared and who have limited skills in other areas.

> *Lots of them, I think, want to go back because it's really high wages…. So, it's mainly about finding them something new, which is, I think, difficult for some. They're not all 100% on board with that. - Key informant #2*

For many workers, who have established skills in stonemasonry and a sense of pride in what they do, re-training in an entirely new area of work that is perceived as menial and repetitive may be unappealing.

> *If you take a tradesman who's worked with his hands all his life, and then you tell him that he can't do any manual labour, or any construction role, there really is very limited options for that guy. … Every guy says the same thing: …, "they don't want me to be happy, all they want to do is get me into a job so they don't have to worry about me." … I've got guys saying, "I don't want to be a truck driver. They're telling me that the only thing I can do is be a truck driver. … I don't want to spend eight hours a day, on my own, thinking about the fact that I might die of silicosis." - Key informant #3*

One key informant (#3) emphasised the importance of clear guidelines from occupational physicians about what is, or is not, an appropriate plan for job modification or re-employment in an alternative industry. The key informant stated that, while one occupational physician said the affected worker must not work in any industry related to construction because of the risk of dust exposure, another said they could go back to stonemasonry so long as they wear appropriate protection.

> *There's just this massive discrepancy, at the moment, between what is and isn't acceptable as ongoing work. - Key informant #3*

> *We don't know what the further exposure is going to do to their progressive disease - it might make no difference whatsoever. They've already got the disease. It's relatively quiescent and it's not going to make any difference whatsoever because they're now exercising safe work practices and all the rest of it. Or … the increments of further exposure tips them over the edge and converts them from a quiescent disease process to an aggressive disease process. Key informant #7*

Return-to-work, compensation and medico-legal issues

Patients with a positive diagnosis of silicosis may lodge an application for workers' compensation; and, once approved, they may access treatment as well as weekly income benefits until they return to work, or a terminal payout if it is unlikely they will return to work.

> *With changed legislation, our big focus moving forward will be on those that do, definitely, have capacity to return to work and employment, and how we progress the return-to-work. - Key informant #2*

Due to the knowledge gaps about silicosis and its pathophysiology, key informants indicated that they take an individual approach to managing compensation, treatment and return-to-work options for workers.

> *A really supportive approach for each individual … that's still a little bit unknown and that we'll have to kind of go with the journey. - Key informant #2*

Key informants highlighted the challenges pertaining to medico-legal issues and compensation, both now and in the future.

> *During the time lag between when we first identify these people with a diagnosable disease but they have yet to actually identify the rate of progression in that particular individual, the anxiety level is sky high as you can well imagine … The issues for that particular group is then all about adjustment to the diagnosis and uncertainty about the rate of progression. And then that is compounded by the compensation environment. - Key informant #7*

> *We're just terrified of being pulled into court in 10 years and saying, "Oh well, he's only progressed in the last decade and you sent him back to this job, so how do we know that he didn't progress because you put him back in this industry?" Key informant #3*

The terminology in this field is also problematic. For example, progressive massive fibrosis (PMF) is being used as a marker for compensation, whereas it was intended as a description of complications.

> *Progressive massive fibrosis, the term was never really intended to be a diagnostic term, it's really a descriptive term. … From a medico-legal and compensatory perspective, and from a WorkCover issue, the patients will get treated differently if they have PMF. They had a more rapid pathway for accessing compensation, and those with PMF tended to be given a poor prognosis and were able to access terminal payouts more quickly than other patients. So, psychologically, this label of PMF was a bit of a disaster. … We're in this medico-legal bind where you've got an asymptomatic 28-year-old with normal lung function, and the lawyer's saying, "Does he meet the definition for a terminal payout, because he's got PMF?" - Key informant #3*

In the experience of one key informant, the possibility of a terminal payout is tempting for some workers, particularly if they perceive limited future employment opportunities.

> *You get a terminal payout, you get your $800,000 and you walk out the door. Now if you ask those guys, "If you had $800,000 this afternoon, what would you do?" the one response that I had about a month ago was, "I would buy a huge bag of drugs and a jet ski." - Key informant #3*

One key informant highlighted the tension between providing optimal treatment and disease management and compensation issues.

> *I'm being frustrated in every which way by the lawyers trying to maximise the damages claim that these people are going to have. Different jurisdictions have different access to the common law damages or the entitlements to different compensation depending on which jurisdiction you're in. … the personal injury common law lawyers are inhibiting the engagement of the individual in the research and the various strategies that might optimise their health outcome because the worse they are, the bigger the payout they get. The worse they are, the quicker they're going to die. You're stopping me from actually working with this individual to actually improve their health. You might get a bigger payout but they're going to live a lot less to enjoy it. …The frustration now that you've got people being essentially motivated to finalise their statutory compensation claim so they get their payout because once they've got their statutory claim finalised, then they can proceed with the common law claim and get the damages bill which is where they get these promises of millions of dollars. Key informant #7*

CURRENT TREATMENT INTERVENTIONS

> *It's either sit on your hands and don't do anything or, at least, give them a bit of oral steroid. One of the most frustrating parts about diagnosing this condition is that we really don't have much else to offer at the moment. - Key informant #5*

Based on published evidence and key informants' experience, a limited range of support and symptom management options are available for patients with silicosis.

Current interventions, which may vary according to different stages of disease progression, include:

Early intervention and support

- Smoking cessation
- Maximising cardiovascular and respiratory health
- Psychological support
- Whole lung lavage

Mid-stage treatment and symptom management

- Anti-inflammatory drug therapy
- Pulmonary rehabilitation
- Managing symptoms and complications

Late-stage treatment options

- Lung transplantation

Early intervention and support

Key points

- Smoking cessation support is critical to immediate health as well as future eligibility for a lung transplant if needed **[Strong support – expert opinion]**
- Cardiovascular and respiratory health: maximising health and fitness is important for minimising the risks of secondary complications **[Strong support – expert opinion]**
- Psychosocial support **[Limited evidence base for silicosis; Strong support – expert opinion]**
    - Although there was limited evidence of effectiveness of psychological support (e.g. cognitive behavioural therapy) for silicosis, it was strongly recommended by key informants
    - Limited evidence supported improving social support to reduce anxiety and depression in silicosis patients
- Whole lung lavage **[Limited evidence base for silicosis; moderate support – expert opinion]**
    - There were mixed effects and conflicting views on whole lung lavage for silicosis
    - Effectiveness of whole lung lavage for silicosis was based on limited studies of patients with moderate-severe silicosis
    - Whole lung lavage removes foreign material from the lung and may alleviate respiratory symptoms in the short term; longer-term outcomes are unknown
    - Whole lung lavage was well-tolerated in most studies, without serious adverse effects, even amongst patients with severe lung dysfunction
    - Key informants differed in their views: Some agreed that whole lung lavage for early stage silicosis would be well-tolerated, with minimal risk of adverse effects; others suggested that it was too risky, or ethically questionable in asymptomatic patients
    - The timing of the procedure may also be important. Patients in early stage disease may potentially gain more benefit, with lower risk of adverse effects.

After prudent avoidance to remove workers from the risks of further silica exposure, key informants agreed that the next steps are to address other physical risks (smoking, poor general health), prevent secondary injury (psychological distress, complications) and reduce the impact of the silica load in patients' lungs, if possible.

> *Basically, it's all about adjustment to injury, adjustment to diagnosis counselling. So, it's counselling in relation to what does this impact upon your employability and deployability, what do they need to do to optimise their respiratory health and hygiene and essentially come to grips with what is a life-shortening diagnosis. - Key informant #7*

Smoking cessation

All the key informants agreed that urging silica-exposed workers to stop smoking was crucial, not only for their immediate health, but also for their future eligibility of accessing a lung transplant if needed.

However, one key informant (#5) suggested that accessing smoking cessation services was problematic.

> *Talking about smoking cessation strategies… which are pretty difficult to access at the moment. They need more than just going onto Quitline and being referred for nicotine replacement. They actually need one-on-one counselling and high-level support. - Key informant #5*

Another key informant (#8), who primarily dealt with end-stage silicosis, explained how smoking impacts on a patient's likelihood of accessing a lung transplant if their disease progresses.

> *Smoking is something that takes away those very numbers that they're going to need every last one of them. I think if you had to name one thing that this group should be avoiding, it's that. We can lose weight, we can do other bits and pieces, but they'll regret every last ml of lung function that's lost - and the addiction that goes with that - is a problem. Because we will not take active smokers full-stop, whatever the cause of their problems, whatever their age. - Key informant #8*

Given the importance of smoking cessation, one key informant (#8) suggested that workplaces could do more to address smoking, so that they are "sorted by the time they get to me [for transplant]".

Maximising cardiovascular and respiratory health

Key informants agreed that maximising patients' cardiovascular health, respiratory health and overall fitness was essential; and monitoring their progress to determine whether the disease was progressing.

> *I'd be wanting to have them as physically fit as they could reasonably be. Making sure they're active. And … if there's any cardiac issue, dealing with that. As part of that maximising their respiratory health, you'd want to make sure they were getting vaccinated, if they're getting the flu shot each year. - Key informant #1*

> *They'd have to have some series of lung function tests ... would help with the monitoring so you can get a feel for whether things are changing quickly or not. Key informant #1*

A key part of improving workers' overall health is increasing their understanding of the disease and what they need to do to maintain good health.

> *Developing the insight and understanding of these people, their general physical conditioning as it relates to the cardiovascular respiratory reserve is really important to optimising their health. We see in a number of these people, a pseudo improvement in their lung function testing because they're now stopping smoking, they're improving their exercise tolerance, they're getting fitter in terms of their cardiorespiratory function and they're developing sufficient insight to understand that, "If I get a common cold, what do I need to do to stop it becoming a complicated upper or lower respiratory tract infection?" The education around respiratory hygiene is a really important component. Key informant #7*

For patients exhibiting respiratory symptoms, key informants suggested that supplemental oxygen, bronchodilators and physiotherapy may be beneficial to manage symptoms.

> *Sometimes it's a case of making sure they've got appropriate oxygenation … it might be bronchodilators, because sometimes with their chronic obstructive pulmonary disease there's a reversible component. Sometimes steroids, and supplemental oxygen, they're probably the main, and physio, just physio probably the mainstays. - Key informant #1*

Psychosocial support

> *You counsel them psychologically and help them to understand that uncertainty is critical. - Key informant #3*

Anxiety and depression are common comorbidities for patients with chronic respiratory illnesses.[21] Based on evidence from the peer-reviewed literature, psychosocial interventions have been undertaken to support patients with chronic lung diseases such as chronic obstructive pulmonary disease (COPD), but few studies specifically examined the effectiveness of psychosocial interventions for silicosis. For example, one systematic review reported small, but significant, benefits of cognitive behavioural therapy to manage COPD-related depression.[22]

Addressing the psychological effects (e.g. anxiety, depression) of coping with a silicosis diagnosis and poor prognosis of the disease was also identified by key informants as critical to the patients' wellbeing.

> *They actually love doing what they do. … They're craftsmen. It's a fairly, from one level, mundane process. But they've taken raw product to create it into something that appears beautiful and is aesthetically appreciated by society. You take that away from them and you've actually further insulted their sense of who they are and what they do. - Key informant #7*

> *The psychological aspect is really big; nearly all the workers I've seen have had major issues in terms of anxiety, insomnia, depression. A lot have had marriage breakdowns and various other stresses related to it. So their psychological support is a really massive component of this. - Key informant #5*

One key informant (#3) described this young cohort of workers as "difficult". That is, many are non-compliant, with a high level of substance use, and unwilling to engage with psychological services.

> *There are those people who are psychologically in high levels of denial so they don't want to actually even admit that they've got a disease and they don't want to engage in any services or compensation structures. They don't even want to engage in ongoing health surveillance because they don't want to know that they're actually going to die. Again, for some people, that is a legitimate psychological coping mechanism and they rationalise it in the sense that the individual, "I've already been exposed. The damage is already done. Just get on with life and I'll just enjoy life. If it means I get further exposure that shortens my life, so be it. That's my choice." - Key informant #7*

Social support, which involves fostering strong social networks and relationships, also demonstrated a positive impact on health and wellbeing.[23] A cross-sectional study of 324 patients (China) with silicosis showed a significant correlation between low levels of social support and higher levels of anxiety and depression, suggesting that improving the levels of social support may contribute to lowering symptoms of anxiety and depression.

Maintaining social connections through the workplace was also identified by key informants as important to their mental health:

> *By complementing that through the exercise, gym-based activity where they are sharing a common utility. They all go to the same gym. They socialise and network. One of the biggest complications of this particular disease is that we are physically removing them from their social networks of support.*
> *Key informant #7*

Key informants noted the importance of credible and trustworthy sources of support for maintaining patients' psychological health.

> *Number one is support. Support from people who they trust and they understand the disease and processes that they're going through. So, that's their close network of treating practitioners who are seeing these people. … As we've grown the cohort, basically, the therapists are developing their insight and understanding to the psychological demands and challenges that this cohort are facing. An educated cohort of psychologists are really important.*
> *Key informant #7*

Workers who can transfer, or re-train, in another industry may be protected from the secondary psychological injury that often accompanies a silicosis diagnosis. However, the key informants suggested that others perceive their prospects as bleak.

> *Often what happens then, is in an attempt to rapidly get them into the workforce, all they do is they just lean on the psychological injury. They say, "Look, I'm just really not in a place, psychologically, where I can even think about re-training."*
> *Key informant #3*

Similarly, psychological services may need to be targeted to this younger cohort. Given the current uncertainty around disease progression if workers are diagnosed early and avoid further exposure, one key informant (#3) recommended that patients should be provided support that focuses less on the poor prognosis of silicosis and more on appropriate re-employment in a silica-free environment and psychological services to address depression.

> *So, the two biggest issues that I face, with the group, it's not really medical problems, it's the psychological injury, because they don't have great coping strategies; and it's weight gain. And, if you look at the weight gain in my cohort it's just phenomenal. I think the most was about 22 kilos in 10 months.*
> *Key informant #3*

> *I know the insurance companies and occupational therapists … they are focused on getting people re-employed, but these guys – at 32 you're old in the factory, you're at the top of your game. … So, they really have a sense of pride in what they do, and to be demoted, in their words, to something that is really menial and repetitive, is just not something that assists them in the long term. They just will not re-engage with a workforce. - Key informant #3*

> *It leaves them both financially and then psychologically and emotionally lost in the communities a bit. They don't know what to do and … to take away the job and everything else, they're in trouble. It's definitely a huge burden and this sense of, even explaining it, what's happened, they're totally puzzled.*
> *Key informant #3*

Whole lung lavage

> *Theoretically we would think if you've got a huge silica load in the lung tissues in the lungs and the airspace of the lungs, if you get rid of that … It might stop it progressing. - Key informant #4*

Overall, whole lung lavage for silicosis patients is somewhat controversial. Mixed effects have been reported in the published literature; and mixed views about the benefits have been expressed by key informants.

First described in the 1960s, whole lung lavage has been used routinely in the treatment of pulmonary alveolar proteinosis (PAP) to wash out the materials that obstruct the alveoli and cause breathing difficulties.[24] Patients are anaesthetised and the lungs are treated sequentially. While one lung is ventilated artificially, the other is perfused with normal saline to dislodge the foreign particles; and the process is repeated for the opposite lung. As there is a risk of hypoxemia in patients with complications or severe respiratory failure, a process of extracorporeal membrane oxygenation (ECMO) may be employed, whereby blood is withdrawn and returned to increase oxygenation and remove carbon dioxide from the blood. However, since PAP is rare, no randomised controlled trials have been undertaken; and no specific guidelines have been developed. Awab et al.[24] provided an overview of the technical details of whole lung lavage.

From a global survey of 30 medical centres that performed 1,110 whole lung lavage procedures for PAP,[25] the following complications were identified:

- Fever (18%)
- Hypoxemia, or abnormally low concentration of oxygen in the blood (14%)
- Wheezing (6%)
- Pneumonia (5%)
- Pneumothorax, total lung collapse (1%).

Although one cardiac arrest and one death were reported (0.01%), overall, the procedure was reported to be safe, well-tolerated and effective, but did not prevent recurrence of symptoms.

Very few published studies were identified that investigated the effectiveness of whole lung lavage for patients with silicosis.

Prudon et al.[26] reported the outcomes of whole lung lavage for two stonemasons with silicosis. Up to four grams of silica were removed from the patients' lungs in the lavage process, without complications; and the authors suggested that removing the silica burden may slow the progression of the disease.

Similarly, a case report described positive outcomes for a patient with complicated silicosis.[27]

Case report[27]

A 44-year-old male with silicosis presented with hypoxemic respiratory failure and severe bilateral swellings or hardened tissue in the lungs. With the support of ECMO, whole lung lavage was performed on the patient involving 6-14 flushes (1 litre warm saline) to the left and right lung, respectively until the drained fluid changed from milky to clear. The patient showed clinical and functional improvement and respiratory failure was resolved without complications. Moreira et al.[27] reported that 17 additional cases of whole lung lavage have been performed at the same centre without complications.

One key informant acknowledged the potential benefit of ECMO in patients with severe lung dysfunction, but suggested that whole lung lavage in a young, reasonably fit silicosis patient was unlikely to present difficulties:

> *That's an option, if you have someone who is so sick, that you cannot ventilate them on one lung. But that's not this cohort. This cohort are otherwise, reasonably well still and will tolerate whole lung lavage without any problem at all, without resorting to ECMO. - Key informant #6*

In addition to the case studies described above, two randomised controlled trials (RCTs), which were undertaken in China, reported that the benefits of whole lung lavage for silicosis patients were sustained for up to four years.[28, 29] However, these articles were published in Chinese and, based on information in the abstract only, it is difficult to critically appraise the work to determine the extent of potential biases in the methods (e.g. selection bias, publication bias).

Key informants also had misgivings about the quality of the Chinese studies as well as the differences in patients compared with the Australian cohort: "There's a lot of missing detail in those studies" and "most of those workers would have self-presented for medical review, because they were symptomatic". (Key informant #6)

> *Until we get multi-centre replication of the research, you have a level of scepticism around how robust is this evidence being used to support a particular treatment strategy or intervention. - Key informant #7*

In contrast, one key informant suggested that a high level of evidence was not feasible for whole lung lavage or other surgical procedures, as it would be difficult to recruit sufficient numbers for a robust clinical trial; nor was it necessary for a surgical procedure for an orphan disease.

> *Those trials [Chinese], they're actually quite large, and they're randomised, whereas most surgical procedures – to determine whether a surgical procedure or surgery is effective - have never been subjected to randomised controlled trial criteria. So you'll never find a randomised controlled trial of appendectomy, for example, versus do nothing. Equally there's never been a randomised controlled trial of leave a foreign body in someone versus remove it. … Nobody would ever do that trial because it just makes common sense, that if someone has a foreign body in place then you should remove it. The thing I find frustrating is that the whole lung lavage is being subjected to a sort of evidence level that is hardly ever required of a surgical slash device or procedural intervention. - Key informant #6*

Despite reservations about the whole lung lavage studies undertaken in China, key informants largely accepted that it was a viable treatment option, particularly for early stage silicosis. They

suggested that, in the absence of an effective silicosis treatment, a safe and well-tolerated treatment to remove silica from the lungs may reduce the potential for ongoing damage.

> *There is an opportunity with the screening programs in Australia that are capturing workers at a stage where I think this [whole lung lavage] could be effective and quite different probably from the cohorts that would start from China. I think, if you put those studies together, I think there is a clear clinical benefit in whole lung lavage and that's in a cohort that's likely to be even more advanced than the average worker in Queensland. - Key informant #6*

> *These guys are pretty young. In the early stages, the lung function is very good, so I think the risk related to it would, actually, be pretty low, if done at a specialised centre. - Key informant #5*

For the most part, key informants acknowledged that, in the hands of an experienced medical team, washing out some of the silica load from the lungs is "an extremely safe procedure" (Key Informant #6) that, 'theoretically', could be beneficial. However, some concerns were raised about the optimal time for the procedure.

> *Well, we know in theory that the earlier you do it, the greater the return in terms of the amount of silica load you get out of the lung. But we still don't know whether it actually makes a difference. That's part of the experimental nature of the whole lung lavage. - Key informant #7*

> *If we wait for them to actually develop the nodular granularity in their lung fields which means that they've got an established disease, it's too late to do a whole lung lavage, to actually try to wash out the silica load. Once it's actually scarred up and embedded in the parenchyma, you can't just wash it out. When do you do the whole lung lavage? - Key informant #7*

In addition, while whole lung lavage may remove dust particles and other inflammatory factors, the long-term outcomes are not known; and sustained improvement has not yet been reliably demonstrated in silicosis patients.[2]

There were also some ethical concerns about performing a whole lung lavage in asymptomatic patients, who may not progress, compared with waiting until progression is observed when the potential opportunity for greatest benefit may have passed.

> *On our basis of the people we've followed for the last – first 18 months with early disease and that's been stable, are you justified in doing a whole lung lavage on those if they're not – you know, where we don't have evidence of progression. But then if they're starting to progress is it too late to do the whole lung lavage to get rid [of it]. If they haven't worked for 18 months, is the silica still sitting in their airway? And it is too late to do a whole lung lavage then. - Key informant #4*

> *But you also want to know (a) it's got to be early, and (b) you wouldn't do it unless there's evidence of some sort of progression but you can't be too late otherwise it's too late to do anything to modify the disease. That's the difficulty there and that's probably some sort of the conflict or the disagreement or the controversial aspect of whole lung lavage. - Key informant #4*

One key informant expressed the need for caution with performing whole lung lavage, indicating that it was a very invasive and potentially harmful treatment:

I would actually much rather use a nebulised treatment rather than a whole lung lavage because whole lung lavage is associated with significant side effects and death even in some people and … you have to have a general anaesthetic, you have to go to an intensive care bed afterwards. - Key informant #9

Mid-stage treatment and symptom management

Key points

Anti-inflammatory drug treatment **[No evidence to support]**

- Despite frequent prescribing of corticosteroids for lung diseases, there is no evidence to support their use for silicosis
- Non-steroidal nasal spray N115 has shown promising results in Phase III clinical trials of patients with pulmonary fibrosis

Pulmonary rehabilitation **[Limited evidence for silicosis; moderate support – expert opinion]**

- Published evidence reported that physical activity resulted in functional improvements in exercise capacity soon after a rehabilitation program commenced, without adverse effects; but was not sustained over the long term without maintenance
- Findings were based on evidence from systematic reviews and meta-analyses of studies with small sample sizes
- Referral to pulmonary rehabilitation services may not be appropriate in all silicosis cases.
- The effectiveness and relevance of pulmonary rehabilitation for younger workers with early stage, asymptomatic silicosis is not known

Managing complications **[Strong support – expert opinion]**

- Individual-based management of complications as needed.

Once patients reach a stage where symptoms, such as reduced respiratory function, become apparent, the lung tissue is likely to show evidence of moderate-severe fibrosis. At this stage, clinicians may consider interventions to improve respiratory function, prevent infections and manage complications (e.g. COPD, arthritis, scleroderma, cancer).

Anti-inflammatory drug therapy

There is some thought that bronchodilators are of some benefit in managing symptoms in people with silicosis, but there's not a lot of evidence for how good that might be. - Key informant #10

Supportive treatments are similar to those used for other respiratory disorders and include cough medicine, bronchodilators, antibiotics for chest infections and corticosteroids to reduce symptoms of bronchitis.[2] In general, these are temporary measures to ameliorate symptoms and complications; however, longer term benefits of these treatments have not been demonstrated for silicosis.[30]

Although corticosteroids have been the most commonly prescribed therapy for IPF, there has been no formal, rigorous examination of its efficacy.[31]

Experimental research

- A recent experimental study showed reduced inflammation and fibrosis in silica-exposed rats that were treated with Infliximab, which inhibits inflammation caused by expression of tumour necrosis factor; however, these results have not been replicated in human trials.[32]
- Cytokines, such as interleukin-1β, are targets for reducing lung tissue inflammation in silicosis and other interstitial lung diseases. While experimental studies have shown reduced fibrotic nodules, and limited case reports have shown improvement in lung fibrosis, this has also not been tested in clinical trials.[2]

Given that the pathogenesis of silicosis and similar fibrosing lung diseases may require more than simple anti-inflammatory or immunosuppressive treatment, corticosteroids are not plausible targets of research investigation.

The key informants agree that anti-inflammatory medications are ineffective:

> *From a medication point of view, inhaler therapy, you know, Ventolin or inhaled steroids, haven't been shown to give any benefits at all. And, it's not really an airways disease, it's more a parenchymal or interstitial lung disease, so inhaler therapy is not effective. I've tried with low dose steroids, but again, it's a pretty data free area, unfortunately. - Key informant #5*

In contrast, Phase III clinical trials of non-steroidal nasal spray N115, which is marketed by EmphyCorp,[e] have shown promising outcomes. Preliminary findings showed that N115 relieved clinical symptoms and improved lung function in patients with interstitial lung diseases.[33] Following treatment with N115, patients experienced:

- Significant improvement in spirometry tests (FEV_1, FVC)[f] and oxygen levels, even after routine steroid medications were reduced or ceased
- Significant improvement in FEV_1/FVC ratio (increased from 52% to 86%)
- Reduced clinical symptoms, such as coughing and congestion.

However, this has not been tested in patients specifically diagnosed with silicosis.

Pulmonary rehabilitation

> *That old approach with older diseases just doesn't work with these young guys. There needs to be a different approach, which is focused on them. If you try putting one or two of these guys in pulmonary rehab with 65-year-old people who are on oxygen, they will never come back again. - Key informant #3*

Pulmonary rehabilitation is a well-established therapeutic approach for patients with respiratory diseases such as COPD.[34] The rehabilitation program comprises a combination of physical exercise sessions (endurance, gymnastics, walking, muscle strength training), breathing exercises, relaxation

[e] https://emphycorp.com/our-products/emphyclear-nasal-copdpf-prescription
[f] See Table 11 (Appendix) for details on spirometry tests.

techniques and nutritional education. Three meta-analyses assessed the effectiveness of pulmonary rehabilitation programs for COPD [35, 36] and interstitial lung diseases;[37] one systematic review evaluated the effectiveness of an exercise program for patients with dust-related lung diseases;[Dale, 2015 #222} and one uncontrolled study investigated the effectiveness of pulmonary rehabilitation for silicosis patients.[34] Table 5 shows findings from these studies.

Overall, for COPD patients, there was evidence of significant improvements in standard measures, such as six-minute walk distance, lung function (VO_2 peak) and some quality of life measures in the short term (immediately after the final session) compared with no-program controls.[36] However, benefits were not sustained over the longer term (up to 12 months); and there was no significant difference in survival rates at six months for patients with interstitial lung diseases.[37] Self-management interventions with action plans for exacerbation of symptoms in COPD patients also reported significant benefits.[35]

For patients with dust-related interstitial lung diseases,[38] the 6-minute walk distance and health-related quality of life (e.g. emotional function domain) increased significantly compared with no-exercise controls after eight weeks of exercise. However, while some improvements were sustained for up to six months after training, the overall findings were inconclusive due to the small sample sizes and poor quality of studies. Larger, well-designed studies are needed to determine whether exercise training reduces symptoms and improves quality of life for patients with silicosis.

One uncontrolled study of patients with occupationally-acquired respiratory diseases included a sub-analysis of 42 silicosis patients who undertook a four-week pulmonary rehabilitation program.[34] Compared with baseline measures, patients showed significant improvements in exercise capacity immediately after the program. At the 12 month follow-up, only benefits of improved strength were sustained; and there were no significant changes in the use of health services (e.g. use of antibiotics, frequency of hospitalisation). The authors suggested that an ongoing rehabilitation program may support maintenance of functional improvement.

Several organisations provide online support for managing symptoms of lung diseases. For example, the US Pulmonary Wellness Foundation offers free webinars[g] for patients with interstitial lung diseases; and an online volunteer support network has been established for patients with IPF.[h]

[g] https://pulmonaryfibrosisnews.com/2020/01/27/pulmonary-wellness-foundation-offers-free-interactive-webinars-with-experts-on-respiratory-health-topics/

[h] https://pulmonaryfibrosisnews.com/2020/02/19/breathe-support-network-aims-bridge-pf-information-gap-raise-awareness/

Table 5. Effectiveness of pulmonary rehabilitation for lung diseases

Reference Country	Study design	Intervention Population	Outcomes
Lenferink (2017)[35] Netherlands	Meta-analysis of 22 RCTs (*N*=3854)	Self-management interventions (various) for patients with acute exacerbations of COPD Controls: no program	After 12 months FU: • Significant improvement in health-related quality of life (respiratory): mean difference -2.69 [95% CI -4.49, -0.90] vs controls • Significantly lower risk of hospitalisation: OR 0.69 [95% CI 0.51, 0.94] • NS difference in other health care utilisation, dyspnoea scores, exacerbations, mortality Programs with a smoking cessation component showed statistically significant improvements vs no smoking cessation
Dale (2015)[38] Australia	Meta-analysis 2 RCTs (*N*=40)	8-week exercise program for patients with dust-related interstitial lung disease Controls: no program	At 8 weeks FU: • Significant ↑ in 6MWD: mean difference 53.8 m [95% CI 34.4, 73.3] vs no exercise controls • Significant ↑ in health-related quality of life (emotional function): mean difference 5.57 [95% CI 2.3, 8.8] vs no exercise controls
McCarthy (2015)[36] Ireland	Systematic review and meta-analysis of 65 RCTs (*N*=3822)	4-52 weeks pulmonary rehabilitation program for patients with COPD Controls: no program	At FU: • Significant improvement across all quality of life domains; effects larger than minimal clinically important difference of 0.5 units: Dyspnoea: mean difference 0.79 [95% CI 0.56, 1.03] Fatigue: mean difference 0.68 [95% CI 0.45, 0.92] Emotional function: mean difference 0.56 [95% CI 0.34, 0.78] • Significant improvement across all respiratory domains: mean difference -6.89 [95% CI -9.26, -4.52] • Significant ↑ in exercise capacity (Wmax): mean difference 6.77 [95% CI 1.89, 11.65] • 6MWD: Significant ↑ mean difference 43.93 [95% CI 32.6, 55.2] vs control
Dowman (2014)[37]	Meta-analysis of 5 RCTs	4-week pulmonary rehabilitation program	At final rehab session FU:

Reference Country	Study design	Intervention Population	Outcomes
Australia		for patients with any type of interstitial lung disease Controls: no program	• Significant ↑ 6MWD: mean difference 44.3m [95% CI 26.0, 62.6] vs control, p<0.05 • Significant ↑ VO_2: mean difference 1.2mL/kg/min-1 [95% CI 0.46, 2.03], p<0.05 • Quality of life: significant ↑ At 6 months FU: • NS difference in any measures vs controls • Survival rate: NS
Ochmann (2012)[34] Australia	Uncontrolled pre/post study	4-week pulmonary rehabilitation program: Physical exercise sessions (endurance, gymnastics, walking, muscle strength training), breathing exercises, relaxation techniques and nutritional education (*N*=42 silicosis patients)*	At 4 weeks FU: • Significant ↑ exercise capacity vs baseline: 6MWD: ↑ from 457.8±75.1m to 477.4±68.7m, p<0.01 Wmax: 108.3±30.2 to 117.6±27.7watts, p<0.01 Quadriceps force: 57.8±20.9 to 73.4±25.4kg, p<0.01 Handgrip force: 71.9±19 to 80.4±17.4kg, p<0.01 • Significant ↓ in anxiety vs baseline: HADS anxiety: 11.8±3.5 to 8.9±2.2, p<0.01 • Depression: NS • Quality of life: NS At 12 months FU: • 6MWD: NS • Wmax, quadriceps force, handgrip force sustained, p<0.01 • Infections, hospitalisations: NS

* sub-analysis of silicosis patients – study included other occupational respiratory diseases; 6MWD = 6-minute walk distance; CI = confidence intervals; COPD = chronic obstructive pulmonary disease; FU = follow-up; HADS = Hamilton depression scale; NS = not significant; OR = odds ratio; RCT = randomised controlled trial; Wmax = ergometer test maximum exercise capacity

Based on interviews with key informants, some expressed doubts about the relevance of the conventional pulmonary rehabilitation approach for silicosis patients. They suggested that younger male patients, who are asymptomatic, are unlikely to attend a pulmonary rehabilitation program that was designed for an older cohort of patients, with advanced stage of disease characterised by poor lung function.

> *We're not dealing with a disabled group of breathless people…. The mean age of my cohort is 32, so these are young guys that go to the gym, they already go to the gym four times a week, and the ones that don't, have no intention of exercising, they just go to the tavern. - Key informant #3*

> *I don't think any of them [studies] have been powered enough to detect any difference, but you know, it's not going to cause any harm, so no problem with doing that. But it's obviously not going to fix the pulmonary problem. Many of these workers are very fit young men … who are used carrying around huge blocks of stone. … We do a lot of pulmonary rehabilitation in our transplant program. And you can get huge gains, but that's normally in someone who's frail to start with. Whereas these guys are not frail, they've got a lung disease. Key informant #6*

> *They'll probably say, "Look, I do way more exercise in the gym, twice a week than I do here". That's not to say that pulmonary rehab is not beneficial, it's hugely beneficial in the right context, but I don't think this is the right context. Key informant #6*

Overall, although there was evidence of benefits of pulmonary rehabilitation for patients with respiratory diseases such as COPD, asthma and some interstitial lung disease, the evidence of benefit for silicosis patients is uncertain as no research was identified for pulmonary rehabilitation for silicosis – particularly amongst a young cohort with early stage, asymptomatic silicosis.

Managing symptoms and complications

Silica-induced impairment of the lung tissue restricts lung function and may lead to complications, such as respiratory infections and other exacerbations.

> *The early cases don't … have any major abnormality of lung function but if they are a bit more advanced, they've got airway symptoms. Then treatment for COPD and other avenues, or treatment of respiratory infection is important obviously. Key informant #4*

> *It's only managing whatever the underlying respiratory exacerbation is. So typically when people are presenting, they're presenting say with an exacerbation of chronic airflow limitation or chronic obstructive pulmonary disease, which may or may not be associated with a lower respiratory tract infection. So it's really about managing of the lower respiratory tract issues. - Key informant #1*

Pulmonary arterial hypertension is another identified complication in silicosis patients.

In one case study,[39] percutaneous pulmonary artery stenting and balloon angioplasty was performed on a 52-year old stonemason with silicosis-induced enlarged hilar lymph nodes and pulmonary artery stenosis. One week after surgery, his clinical symptoms improved and his 6-minute walk distance increased from 390m to 450m.

Although short-term follow-up showed positive outcomes for this patient, this is a rare complication of silica exposure and no other studies were identified. Therefore, the potential adverse effects and longer-term outcomes are unknown.

Late-stage treatment options

Key points

Lung transplant **[Limited evidence base for silicosis; moderate support – expert opinion]**

- Lung transplants are the only option for patients with end-stage silicosis
- While the number of published cases was small, lung transplant patients experienced improved lung function and better survival rates compared with similar patients who did not receive a transplant
- Early referral to a transplant surgeon enables earlier planning and preparation, such as smoking cessation and weight control; and may avoid the surgical challenges associated with transplanting severely fibrosed lungs.

Lung transplantation

For patients with advanced or end-stage silicosis and with no further pharmacological options, lung transplantation is the only treatment option.[40] While the study numbers are small, due to the scarcity of patients and availability of donors, patients with end-stage silicosis who received a lung transplant gained significant benefits in terms of lung function and survival.

In one retrospective study with wait-list controls, patients with end-stage silicosis demonstrated significant improvements in lung function and 6-minute walk distance after unilateral lung transplant surgery; and significant increase in median survival.[41] Table 6 provides details of findings.

Table 6. Effectiveness of lung transplant surgery in silicosis patients

Reference Country	Study design	Intervention Population	Outcomes
Sidney-Filho (2017)[41] Brazil	Retrospective cohort study	Unilateral lung transplant 26 patients with end-stage silicosis Transplant group (*N*=16) Wait-list controls (*N*=10)	At 12 months FU: Significant improvement in lung function tests: • FEV_1 ↑ from 1.85±0.97 to 2.14±1.13, p=0.039 • FVC ↑ from 2.22±1.16 to 3.08±1.58, p<0.002 • FEV_1/FVC ↓ from 83.4±9.2 to 71.2±37.6, p<0.01 Significant improvement in 6MWD: • ↑ from 267.4±104.5m to 502.6±78.9m, p=0.001 Compared with wait-list controls: • Significant ↑ in median survival: 3.35 years [95% CI 0.16, 14.38] vs 0.78 years [95% CI 0.12, 3.65], p=0.001

6MWD = 6-minute walk distance; CI = confidence intervals; FEV_1 = forced expired volume in first second; FVC = forced vital capacity; FEV_1/FVC = % of vital capacity in first second (see Table 11, Appendix for details of spirometry measures)

In one small study of five end-stage silicosis patients who underwent lung transplant, three reported good quality of life and were able to return to work.[42] The other two patients died of complications; one at eight days and the other at seven months post-surgery.

One study with matched controls suggested that the survival rate amongst lung transplant patients with occupationally-acquired lung disease was similar to those with other lung diseases.[43]

In contrast, one key informant indicated that lung transplants for silicosis were more challenging than for other indications:

> *Silicosis, the success rate is just not that high, it's just harder to make the whole thing work… It's the absolute edge of the technologies that we can do. It doesn't give as good an outcome as a normal transplant, which is still not a perfect outcome. … A lung transplant normally would be five days in ICU, for silicosis it could be two to three weeks in ICU. A normal person has three weeks in hospital, a silicosis patient could be anywhere between three and six weeks or more in hospital, depending on complications. [Then] they've got an aggressive several months of rehabilitation here … going backwards and forwards to the hospital three times a week for the next two months after that. - Key informant #8*

Information from the UK Open Access Government website[44] suggested that bilateral lung transplant has a better median survival rate of 5-6 years (30% 10-year survival) compared with single lung transplant (12% lower survival at five years). This was confirmed by a key informant:

> *For this condition, if the lungs are not ridiculously advanced and calcified, then doing a bilateral is still the best, particularly in a younger person. But we've been forced to do single lungs where there's just concrete. … The surgeons have said after 10 hours, 12 hours, 14 hours operating: "I'm having trouble on this side, I'm not going to go on for another 10 or 14 hours". … Two lungs would give you 100 percent function back and about 20 percent lung function that we start at. One lung will give you back 65 or 70, because you do the worst one and there's still a bit left from the other. - Key informant #8*

One key informant also highlighted the challenges associated with end-stage disease; and the need to consult with a lung transplant surgeon at an earlier stage, before the stiffening of the lungs makes surgery more difficult.

> *The ones that are progressing, I would have liked to have seen them all earlier because we've had some really late referrals that are just very sad cases, and you're thinking "oh my god, how are we going to do this? There's literally like a concrete block there. - Key informant #8*

Consultation at an earlier time-point would also allow time to prepare the patient and plan a strategy towards lung transplantation:

> *I don't want to see them when they're on oxygen with severe pulmonary hypertension and concreted lungs. I need to be seeing them earlier and plotting our strategies. Because the end-stage ones are desperate and very, very challenging. - Key informant #8*

> *I'm their backstop, so they need to be able to be headed towards a frame that I can work with them. From that point of view, it's about the obvious things of they need to be non-smoking, they need to be of a weight that's plausible, so when you've got no lungs you don't want to have your Body Mass Index too high. They need to be part of a sort of rehab program, and … they need to have their*

psychology sorted. … These people need virtually an allied health multidisciplinary view of making sure that they've got all the other things in line.
Key informant #8

Compliance with the stringent requirements before and after transplantation was noted as challenging:

There's a criteria to getting on the waiting list, not just how sick you are, you've got to be a committed non-smoker, you've got to agree to the rehab, you agree to take all the drugs. There are some people who can't do that, that's obvious and there are some people who start that way - start being compliant and then sort of ironically get so well that they then forget about it, and then start to let things drift and push appointments back and everything else. - Key informant #8

One key informant queried the lack of referrals for transplant, despite the numbers that were predicted through the screening program.

I'm hearing the noise the tidal wave's coming, but I'm not actually seeing it.
Key informant #8

It is possible that this may be related to the early stage at which workers are diagnosed; and the variability or uncertainty about the rate of disease progression once workers are removed from the exposure.

EMERGING TREATMENTS

It is challenging, the idea of repurposing. Nintedanib and the Pirfenidone, they're drugs that are used, so I can't believe that people wouldn't be using them off-label already in patients. Even though there's now quite good evidence of their effects on disease progression in IPF, so why wouldn't you try them in somebody who's got silicosis, when we really don't have anything that's having any impact at all. - Key informant #10

Key points

Antifibrotic therapy **[Limited evidence for silicosis; moderate support – expert opinion]**

- Two antifibrotic drugs have been approved for treatment of IPF: Nintedanib and Pirfenidone
- Clinical trials have demonstrated that they are safe and well-tolerated by IPF patients, with only mild gastrointestinal side effects
- Clinical trials have shown that both drugs are effective for reducing the rate of decline in lung function in IPF patients
- Ongoing clinical trials are investigating longer-term outcomes in patients with dust-related lung diseases including silicosis.

Cell-based therapy **[Insufficient evidence]**

- Phase I clinical trials showed that mesenchymal stem cell therapy is safe and well-tolerated by patients with silicosis or IPF
- Findings from experimental studies demonstrated reduced inflammation and fibrosis in the lungs of silicotic mice
- Preliminary results from inhalation of lung spheroid cell secretomes and exosomes have shown promise in reducing lung fibrosis in silicotic mice
- Larger Phase II and III clinical trials are needed before determining the effectiveness of cell-based therapies for treatment of silicosis.

Antibiotic drug therapy **[Insufficient evidence]**

- Azithromycin (AZT) treatment may be used prophylactically to reduce infection rate in patients with silicosis and IPF
- Experimental evidence suggested that AZT may reduce lung damage by killing fibroblasts that promote fibrosis; however, this has not yet been tested in clinical trials

Other treatments **[Insufficient evidence]**

- Limited evidence showed that Thymalfasin, an immunomodulatory agent, enhanced the immune response; and tetrandrine, a herbal alkaloid, reduced fibrosis in silicosis patients
- Clinical trials are needed to confirm the efficacy of these approaches.

Antifibrotic drugs are at the most advanced stage of all emerging drug therapy options.

Since current treatment options primarily manage symptoms and do not halt or reverse disease progression, research has focussed on therapies with the potential to provide longer-term benefits. In general, drug therapies for silicosis are still in experimental stages or early clinical trials to determine safety and tolerability; and have not yet shown robust clinical effectiveness. However, there are some promising areas for both experimental research and clinical trials.

Experimental research on silicosis has had many challenges, including establishing an optimal experimental model. For the most part, the benefits demonstrated in experimental models of silicosis have not translated to human clinical trials. In experimental rat or mouse models, treatment is often applied soon after fibrosis has been induced. Therefore, it is not clear whether the treatment would be effective in clinical cases where fibrotic tissue has been present in a patient for an extended period.

> *You give a drug as the fibrosis is developing or the silicosis is developing and it really is not mimicking the clinical situation at all, because people have already had the exposure. So there's no point in doing simultaneous treatment at the same time as you're giving the insult. - Key informant #10*

One interesting approach to inducing silicosis in an experimental model is the use of 'fresh' silica dust on human lung tissue, as it more closely resembles the profile of exposure. However, this is still in early stages of development:

> *There's a fair bit of interest that the most damaging silica is fresh. Key informant #10*

Antifibrotic drug therapy

Alveolar inflammation induced by inhalation of RCS triggers fibrosis that leads to secretion of high levels of extracellular matrix and stiffens the lung tissue.[45] Antifibrotic drugs have anti-inflammatory properties and inhibit the proliferation of fibroblasts that are involved in lung tissue scarring. They have been investigated in several animal models of IPF, systemic sclerosis, rheumatoid arthritis and silicosis, with significant reductions in lung fibrosis and inflammation. For example, *in vivo* studies in mice with silica-induced lung inflammation showed that daily doses of Nintedanib significantly reduced the factors (neutrophils, lymphocytes, cytokines) associated with inflammation and fibrosis,[46, 47] thereby potentially slowing the progression of fibrotic lung diseases like silicosis.

A recent study has shown that changes in the blood levels of surfactant protein-A can be used as a biomarker of response to antifibrotic treatment,[48] which may help guide management of IPF and silicosis.

Clinical trials of Nintedanib and Pirfenidone

In human studies, two drugs have been approved for treatment of IPF: Nintedanib (marketed by Boehringer Ingelheim as Ofev) is a tyrosine kinase inhibitor; and Pirfenidone (marketed by Genentech as Esbriet), which has antioxidant effects.[49] Both drugs down-regulate growth factors that are implicated in the development and progression of fibrosis.[50]

Several clinical trials to investigate the efficacy and effectiveness of antifibrotic therapy for IPF or interstitial lung diseases have been undertaken or are currently underway (Table 7).

In a Phase III clinical trial (INBUILD) of 663 patients with progressive interstitial lung disease, patients who received Nintedanib (150mg twice daily for 2 years) had a significantly lower mean rate of decline in lung function tests compared with placebo controls; and the between-group mean

difference in forced vital capacity (FVC) was 107 ml per year ($p<0.001$).[51]. Diarrhoea was commonly reported in patients treated with Nintedanib (67% vs 24% in placebo controls).

Pooled data from six clinical trials of Nintedanib (TOMORROW and INPULSIS trials) for patients with IPF showed that one daily dose (150mg) was generally safe and well-tolerated.[52] The main adverse events were gastrointestinal upsets, particularly diarrhoea in the Nintedanib group (76.5 events vs 25.6 events per 100 patient exposure years in placebo group). For most patients, side effects were managed by treating symptoms, reducing dosage, or temporarily halting treatment; thereby enabling patients to continue treatment over the longer term. Other adverse effects included: elevated hepatic enzymes (12.1 vs 3.4 events per 100 patient exposure years) and cardiovascular events (3.7 vs 1.1 per 100 patient exposure years). Based on mortality data reported in the trials, survival rates were estimated to be higher in the Nintedanib group (11.6 [95% CI 9.6 – 14.1 years]) compared with the placebo group (3.7 [95% CI 2.5 – 5.4 years]). Although caution is needed as there are limitations with extrapolating survival data, the pooled data suggested that antifibrotic therapies have the potential to extend life expectancy for patients with IPF.

Overall, both Nintedanib and Pirfenidone were deemed safe and effective in slowing the rate of decline in lung function and progression of lung fibrosis in IPF patients.

A trial to determine safety and tolerability of Ninedanib in silicosis patients (NiPPS) is expected to be completed in 2025.

Table 7. Summary of trials of antifibrotic drug therapy

Trial	Details	Trial outcomes	Reference
INBUILD trial	Phase III RCT for 663 patients with progressive fibrosing interstitial lung disease Nintedanib 150mg twice daily for 2 years Completed (153 sites in 15 countries)	At 2 years FU: • Significant ↓ in annual rate of decline in ling function (FVC): -80.8 mL/year (Nintedanib) vs -187.8mL/year (placebo); mean difference 107.0mL/year [95% CI 65.4 – 148.5], p<0.001 • Lung function decline slowed by 57% with Nintedanib Adverse events: • Most common was diarrhoea in 67% of Nintedanib group and 24% of placebo group	51, 53 https://clinicaltrials.gov/ct2/show/NCT02999178?term=NCT02999178&draw=2&rank=1
INPULSIS™ trials	2 x Phase III RCTs for 1,066 patients with IPF Nintedanib 150mg twice daily for 2 years Completed	At 2 years FU: • Lung function decline slowed by 50% with Nintedanib • INPULSIS™-1: FVC -114.7mL (Nintedanib) vs -239.9mL/year (placebo), p<0.05 • INPULSIS™-2: FVC -113.6mL (Nintedanib) vs -207.3mL/year (placebo), p<0.05	54-56
TOMORROW TRIAL	Extension of INPULSIS trial for longer-term treatment outcomes Open label: up to 86 months FU	At 52 weeks FU: Significant ↓ in annual rate of decline in lung function: FVC -125.4mL/year (Nintedanib) [95% CI -169.1 to -189.7] vs -189.7mL/year (placebo) [95% CI -229.8 to -149.6], p<0.05	57, 58
INSTAGE clinical trial Efficacy and safety of Nintedanib co-administered with	2 x Phase III RCTs for 274 patients with IPF Nintedanib 150mg twice daily +/- 20mg Sildenafil 3x daily for 24 weeks	At 24 weeks FU: NS difference with addition of Sildenafil	59

Sildenafil in idiopathic pulmonary fibrosis patients with advanced lung function impairment	Co-administration of Sildenafil aimed to lower the pulmonary artery pressure and improve respiration Completed		
INJOURNEY trial of Nintedanib with add-on Pirfenidone	RCT for 105 patients who had completed 4-5 weeks of Nintedanib (150mg 2x daily) Co-administration of Nintedanib (150 mg 2x daily) + Pirfenidone (801mg 3x daily) Nintedanib (150 mg 2x daily) alone in an open-label manner for 12 weeks	At 12 weeks FU: Slower rate of decline in combination therapy: Change from baseline FVC: 3.6ml/12 weeks (increase) (Nintedanib + Pirfenidone) vs 248ml/12 weeks (decrease) (Nintedanib alone) Higher % gastrointestinal side effects in combination therapy: 69.8% (Nintedanib + Pirfenidone) vs 52.9% (Nintedanib alone)	[60]
SENSCIS™ trial (Safety and Efficacy of Nintedanib in Systemic SClerosIS)	Phase III RCT for 520 patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) Nintedanib 150mg twice daily for 2 years Completed	At 52 weeks FU: Significant reduction in rate of decline in FVC: −52.4 ml/ year (Nintedanib) vs −93.3 ml/ year (placebo); difference: 41.0 ml/ year; [95% CI, 2.9 - 79.0], p = 0.04	[61]
PINTA trial (safety and efficacy of GLPG1205 for patients with idiopathic pulmonary fibrosis	Phase II RCT for 69 patients with IPF GLPG1205 2 capsules, 1x daily x 26 weeks vs placebo Completion: August 2020	Data not available	https://clinicaltrials.gov/ct2/show/NCT03725852
PEARL trial (safety and efficacy of Pirfenidone treatment in Hermansky Pudlak Syndrome (HPS) - Related Interstitial Lung Disease (ILD)	Phase II single arm clinical trial for 50 patients with HPS-ILD Perfenidone 803mg 3x daily for 3 years Completion: December 2022	Data not available	https://clinicaltrials.gov/ct2/show/NCT04193592?term=pirfenidone&draw=2&rank=1
The Nintedanib in Progressive Pneumoconiosis study	Single arm clinical trial 100 patients with coal pneumoconiosis,	Data not available	https://clinicaltrials.gov/ct2/show/NCT04161014

(NiPPS): A collaborative NSW treatment trial (NiPPs)	asbestosis or silicosis Nintedanib 150mg twice daily for 3 years Completion: February 2025		
Safety, tolerability and pharmacokinetics of Caveolin-1-Scaffolding-Protein-Derived Peptide (LTI-03)	Phase 1 clinical trial 56 healthy volunteers Ascending doses of Caveolin-1-Scaffolding-Protein-Derived Peptide (LTI-03) Completion: August 2020	Data not available	https://clinicaltrials.gov/ct2/show/NCT04233814

CI = confidence intervals; FU = follow-up; FVC = forced vital capacity; GLPG1205 = small molecule designed to specifically block the activity of GPR84, a protein that drives chronic inflammation; RCT = randomised controlled trial

Antifibrotic treatment for early stage lung disease

Importantly, although most clinical trials recruit patients with moderate-severe lung dysfunction, evidence showed that the rate of decline was also reduced in patients with preserved lung volume (i.e. less impairment), which indicates it may be beneficial as an **early treatment option** for patients with lung diseases.[62]

However, one key informant expressed concern about treating mild cases of silicosis with antifibrotic agents; and emphasised the need for appropriate controlled studies.

> *When you go to less severe disease and you're using a toxic agent, you're exhibiting a level of faith that the outcome as a result of the intervention is going to be better for the majority than the outcome if you didn't do it. … We need a number of cases that we can document and monitor and at one level do the case-controlled trials where there's a treatment group and a non-treatment group … obviously the blinded trials would be ideal but the reality is that people are going to die while we wait for this information. - Key informant #7*

Restrictions and accessibility

Restrictions on reimbursement for antifibrotic drug therapy may have a detrimental effect on outcomes for patients with IPF as well as healthcare utilisation costs.[63, 64] Despite evidence that patients with both preserved (FVC>90%) and impaired (FVC<90%) lung function responded to antifibrotic drug therapy, reimbursement for treatment is restricted in many countries (e.g. reimbursement threshold for FVC is 50-90% in Finland). Lassenius et al.[63] retrospectively examined the medical records of 266 Finnish patients with IPF to determine the FVC decline, mortality and healthcare use over the period from 2005 to 2017. Of these patients, 24 percent had mild lung impairment (FVC>90%) and were not eligible for antifibrotic therapy reimbursement. Analyses showed that for every one percent reduction in FVC, there was a four percent increase in mortality. Lassenius et al.[63] reported 14 deaths in patients initially categorised as having mild impairment. Given the progressive nature of the disease, the authors suggested that the reimbursement restrictions were not conducive to early intervention.

Analyses of data from 1,218 cases in the US Pulmonary Fibrosis Foundation Patient Registry showed that approximately 40 percent of eligible patients were not prescribed antifibrotic medication.[65, 66] Among those using antifibrotic medication, less than ten percent had mild lung impairment (FVC>90%) and almost 15 percent had severe lung impairment (FVC<50%). In addition, patients were more likely to use antifibrotic medications if the time since diagnosis was longer. Holtze et al.[66] suggested that health care providers were prescribing antifibrotic treatment primarily for patients with severe impairment and deferring prescribing in those with mild impairment, despite evidence of significant slowing in the rate of lung function decline at any stage of the disease.[66]

Restrictions on the use of antifibrotic therapy for Australian silicosis patients were also highlighted by a key informant.

> *To access that [antifibrotic drugs] would have to be through a clinical trial, or through compassionate use from pharmaceutical companies, it's not PBS-indicated for silicosis. So again, it's something that certainly has merit, but limitations from a treatment point of view of how we can actually access it. Key informant #5*

Other antifibrotic agents

Two other antifibrotic drugs have recently been developed and are undergoing Phase I clinical trials to determine safety and tolerability:

1. CRV431 (Hepion Pharmaceuticals), which is a derivative of cyclosporine, selectively targets and inhibits cyclophilin proteins that are involved in the formation of extracellular matrix. Preliminary data have shown that CRV431 reduced collagen and fibronectin production, which are involved in the process of fibrosis.[67] Currently, CRV431 is undergoing Phase I clinical trials to establish safety.
2. Caveolin-1-Scaffolding-Protein-Derived Peptide (LTI-03) has demonstrated reversal of fibrosis in mouse lung tissue. Currently, Phase I clinical trials are being undertaken in healthy volunteers to determine safety, tolerability and optimal dosage, with the ultimate aim of reversing lung fibrosis.[68]

Experimental antifibrotic drug therapy

- Monash's Biomedicine Discovery Institute is currently undertaking a research study on Relaxin as a potential treatment for occupational lung diseases like silicosis.[69] This study is still in the experimental stage. Relaxin, a pregnancy hormone that has shown antifibrotic effects in kidney and heart tissue, is being investigated as a potential treatment for silicosis. Animal models have shown that Relaxin can reverse lung fibrosis.[70]
- While IPF is diagnosed primarily in humans, it is also recognised that West Highland terriers are prone to this condition.[71] In 2019, researchers commenced a six-month pilot trial of Sobetirome, a thyroid hormone agonist that inhibits lung fibrosis in experimental mouse models. In the dog trial, ten West Highland terriers diagnosed with IPF are given daily doses of Sobetirome and outcomes are measured by CT scans. This trial is expected to finish in March 2020.

Cell-based therapy

While antifibrotic drugs may slow disease progression, they are not curative. Therefore, cell therapies to regenerate damaged tissue have emerged as another area of investigation.

Cell-based therapies for chronic lung conditions have advanced rapidly in the past ten years. In particular, mesenchymal stem cells, which are derived from a variety of sources (e.g. lungs, adipose tissue, blood, bone marrow, umbilical cord) have the capacity to differentiate into alveolar epithelial cells.[72] Moreover, mesenchymal stem cells are 'immune privileged', which means cells can potentially be harvested from an immunologically incompatible donor (allogeneic), without adverse reaction. Experimental studies using lung disease models have shown that mesenchymal stem cells preferentially target areas of inflammation. For example, preclinical studies of experimental silicosis showed that bone marrow-derived cells (mononuclear or mesenchymal) reduced inflammation and fibrosis in silicotic mice.[72]

To date, encouraging results from Phase I clinical trials have reduced concerns about safety and tolerability of cell therapy for IPF and silicosis.[50] Although only small uncontrolled pilot studies with fewer than 10 silicosis patients have assessed the efficacy of cell therapies for slowing disease progression, early results are promising, with no measurable decline in lung function or adverse effects after treatment.

In a meta-analysis of 23 clinical studies (controlled and uncontrolled), Zhao et al.[73] reported that infusions or injections of mesenchymal stem cells were both safe and well-tolerated for patients

with respiratory diseases. Examples included intrabronchial injection of autologous bone marrow-derived mononuclear cells into the lungs of five silicosis patients;[74] intravenous doses of placental-derived mesenchymal stromal cells in eight patients with moderately severe IPF;[75] and intravenous doses of mesenchymal stem cells combined with hepatocyte growth factor in four silicosis patients.[76] Studies reported improved lung function,[74] which was sustained for up to 12 months; and all studies reported only transient mild adverse effects (e.g. mild wheezing post infusion).[74]

One study, which combined mesenchymal stem cells with hepatocyte growth factor, also reported a small reduction in the lung nodules (CT scans) at 12 months follow-up.[76] However, while these results are encouraging, authors do not claim that the combined stem cell/growth factor treatment reverses damage. A larger, placebo-controlled trial is needed to determine effectiveness and long-term safety of this approach.

ReCell, a Phase 1 RCT involving multiple intravenous doses of mesenchymal stem cells for patients with IPF has not yet started recruiting patients.[50]

Experimental cell-based therapy

- Preliminary results in a silica-induced mouse model have shown that inhalation of lung spheroid cell secretomes and exosomes led to significantly larger reduction in lung fibrosis compared with usual mesenchymal stem cell treatment (26% vs 17%).[77] Lung spheroid cell secretomes and exosomes, which secrete beneficial proteins and growth factors, have the potential to regenerate normal alveoli and decrease collagen accumulation and myofibroblast proliferation. While it is very early in development, this approach is a promising and less invasive treatment for patients with progressive fibrosing lung disease
- Human granulocyte-macrophage colony–stimulating factor (GM-CSF), which is a glycoprotein secreted by macrophages and fibroblasts, has also shown promise in blocking collagen deposition in mouse models of IPF. However, no human clinical trials have been identified.

Overall, while results from experimental studies are promising, there are many challenges that need to be addressed. Mechanisms are not well understood; and the optimal source of cells, route of administration, number and timing of treatments and dosing intervals have yet to be determined.[50] Even in animal studies, there are issues to resolve. For example, in experimental models that induce fibrosis in animals, it has been argued that the stem cell treatment reduces the inflammatory cascade, rather than reversing fibrosis; thereby limiting its applicability for human IPF in the clinical setting. Larger, controlled clinical trials are also needed to assess the longer-term effects and therapeutic potential before this treatment can be implemented with confidence.

Despite the current lack of evidence from robust clinical trials, stem cell-related businesses market their products aggressively for a wide variety of conditions that have limited treatment options for patients. Appropriate oversight is needed to avoid potential harm from misuse of unproven treatments.[50]

Antibiotic drug therapy

Azithromycin (AZT) is an antibiotic that also has anti-inflammatory and antifibrotic effects. A recent *in vitro* study showed that AZT selectively promoted cell death in the fibroblasts that are responsible for promoting scar tissue in the lungs, without destroying normal healthy fibroblasts.[78] While this is a promising avenue of research, it needs to be tested in clinical trials.

Recurrent infections are common in IPF and other chronic lung diseases and may be considered a marker of disease progression.[79] A retrospective study on the benefits of prophylactic AZT (250mg 3x/week) amongst 103 patients with IPF showed that hospital admissions reduced from 31 (0.29±0.62 per patient-year) in the 12 months prior to the study to seven (0.08±0.3 per patient-year) in the following 12 months. In addition, antibiotics prescribed for infections reduced from 176 courses (1.65±1.70 per patient-year) in the previous year to 40 courses (0.44±0.8 per patient years) in the following year. However, the treatment did not significantly reduce patients' decline in lung function over this time. The prophylactic AZT treatment was generally well-tolerated, with only minor side effects (gastrointestinal upset) reported in 6.5 per cent or patients.

While appropriate prospective controlled trials are needed to confirm these findings, prophylactic AZT may be of benefit in reducing health service use for patients who experience multiple infections over the course of their disease.

Immunomodulation

Exposure to RCS not only induces an inflammatory response by activating alveolar macrophages, but also inhibits immune responses. Xiong et al.[80] showed that patients with silicosis (*N*=80) had significantly lower levels of T-lymphocytes (CD3+, CD4+ and CD8+ cells) in peripheral blood compared with healthy volunteers.[80] This reflects significant immune dysfunction that leaves silicosis patients at higher risk of infection. In this study, silicosis patients were randomised to Thymalfasin treatment or control groups. Thymalfasin is an immunomodulatory agent that has been used to enhance the immune response in hepatitis and cancer. One week after a single dose of Thymalfasin (1.6mg), there was a significant increase (23.4%) in CD4+ cells compared with baseline (381.1±228.6 to 473.7±194.5, $p<0.05$). CD4+ cells are 'Helper' T-cells that regulate immune response. However, there was no significant difference in CD3+ or CD8+ cells. While these results are positive, it is not known whether the increased T-cell count is maintained over time, or whether repeated dosages are required. Further clinical trials are needed to determine the efficacy of this approach.

Currently, a Phase II RCT[i] is underway to determine the safety, effectiveness and dose profile of RVT-1601 (Respivant), which is a non-steroidal, anti-inflammatory drug (sodium cromoglycate) that has been used to treat asthma and is delivered by nebulizer to treat chronic cough in IPF patients (*N*=180). The trial is expected to be completed in December 2020.

Herbal treatment

Tetrandrine is a herbal alkaloid calcium channel blocker that has demonstrated reductions in lung fibrosis in a rat model of silicosis.[81] Tetrandrine has been used in Chinese medicine to treat pneumoconiosis and has been approved by the Chinese Drugs Administration;[2] and acetylcysteine is used to loosen mucous in the airways. However, limited robust clinical trials have tested its efficacy.

In one controlled study of 196 patients with silicosis,[81] control patients (*N*=108) were given anti-inflammatory medication, cough and asthma relief as needed; and 88 patients in the treatment group were given tetrandrine (3x daily x 6 days/week); and acetylcysteine tablets (1-2 x daily) over three months.[81] At eight months follow-up, the proportion of patients whose lung texture (by chest x-ray) improved was significantly higher in the treatment group compared with controls (66% vs 45%, p=0.004); and the proportion that showed no signs of improvement was significantly lower in the treatment group (3% vs 21%, $p<0.001$). There was no significant difference between groups in the proportion of patients experiencing adverse effects (e.g. itching, nausea). Compared with

[i] https://au.scenictrial.com/#!/

controls, the treatment group also showed significant improvements in lung function tests (by spirometry[j]; FVC↑17% vs 7%; FEV_1↑21% vs 4%, p<0.001); and levels of interleukin-6 (↓37% vs 14%, p<0.001) and tumour necrosis factor-α (↓18% vs 9%, p=0.002). The treatment group increased the 6-minute walk distance test by approximately 50 metres, whereas there was no change in the control group (p<0.05). While these findings are promising, they need to be replicated in further clinical trials.

With respect to tetrandrine, one key informant stated:

> *Very exciting opportunity but we don't know yet whether or not the particular product is going to work in more than a few select cases. …It needs much more research to better understand it. It is quite an exciting development.*
> *Key informant #7*

Other experimental approaches

Other approaches, which have shown positive effects in experimental models, include: suppressive oligodeoxynucleotides, interferon gamma, methyl palmitate, N-acetylcysteine, chemotherapy drugs (e.g. Dasatinib) and gene therapy. However these have not yet progressed to clinical trials.[2]

Since silicosis is a rare disease, the number of patients needed for a clinical trial is difficult to achieve; and it is unlikely to attract investment from the pharmaceutical industry. Therefore, our key informants suggested a number of ways to leverage on existing knowledge and drugs developed for other diseases; and to advance our knowledge about silicosis without investing in large clinical trials.

> *The trouble with the pharma approach is that the market is pretty small for silicosis. So unfortunately these guys are going to suffer because it's an orphan disease. - Key informant #6*

A key aspect of treatment for silicosis is characterising the unique mechanisms that underpin the disease pathway. A clearer understanding of these mechanisms will enable researchers to identify novel targets for drug therapy that may have the potential to minimise or reverse the damage.

> *[There is] this proteomics profile where you get all the different components of the extracellular matrix, which extends way beyond collagen - there's hundreds of different types of proteins - and do bioinformatics to determine what's different about the profile of fibrosis in IPF versus silicosis and that may identify targets that we haven't previously considered. - Key informant #10*

> *There are new technologies now that mean you can interrogate lung cells for example, like never before and work out which transcripts are abnormally expressed inside some of the key lungs cells, and work out personalised care basically. - Key informant #6*

For example, it is possible to use what is known about the drugs developed for IPF and identify those with features that are likely to be effective for silicosis.

> *We should be taking exactly the same approach that has been taken in IPF … and that is to apply these breakthrough medical technologies to really accelerate drug discovery. So the key one of those is single cell RNA sequencing. … There's several groups around the world, who've taken that approach, to describe what cells look*

[j] See Table 11 in Appendix for details on spirometry

like in pulmonary fibrosis and compare them to normal cells. And that way, you can see all the transcripts that are abnormally expressed and that way you can then target therapy, work out which transcripts are the ones that are driving the disease. - Key informant #6

We'll have that sequencing data within a few weeks. If we see the macrophage population that we know exists in other forms of fibrosis, then there's already actually a large pipeline of drugs being developed by a global pharma targeting the transcript that I'm talking about. And so they'll become much more interested in targeting silicosis because we'll be able to show that it's highly likely that their drug will be effective. - Key informant #6

For [orphan] diseases, that's the way forward and the FDA has acknowledged that, so you do not now have to conduct massive clinical trials because you know very little about the disease pathogenesis, it is now possible to be very precise about disease pathogenesis and, therefore you can narrow down and target your drug discovery. So it's very very helpful for diseases where there simply aren't thousands and thousands patients ready to take part in clinical trials rapidly. Or the money to do so because there is no market. - Key informant #6

However, most key informants expressed frustration at the lack of funding to pursue potential treatment options:

At the moment we've got potential options but no funding to do anything. Our hands are tied. - Key informant #4

TREATMENTS NOT SUPPORTED

There have been some workers wanting to try some different things, and different types of natural weeds and the like. Our respiratory physicians have been quick to say, "Mate, that's not the way to go." - Key informant #2

Key points

- There is no evidence to support complementary and alternative therapies, such as salt therapy, for silicosis or other chronic respiratory disorders
- Other treatments, including aluminium therapy, polyvinyl-pyridine-N-oxide and thrombulin, are not supported by evidence

There are many dubious claims about the benefits of natural remedies[k] for silicosis. Despite marketing claims, treatment approaches based on complementary and alternative medicines have not been well-researched; and there is no evidence to support their claims of success.

Salt therapy

While there have been anecdotal reports about the benefits of salt therapy sessions,[82] whereby patients sit in a room with a machine (halogenerator) that disperses small salt particles into the air, there is no evidence to support it. A review of 151 articles about salt therapy for COPD reported that only four studies included controls, study quality was poor and there were too many confounding factors and lack of information to attribute any benefits to the treatment.[83] The Asthma and Allergy Foundation of America[l] does not support salt therapy as a treatment, warning that the treatment is expensive and patients may stop taking their regular medications to enable them to afford it. Moreover, there are potential side effects that may exacerbate respiratory conditions. For example, the warm environment may encourage growth of bacteria that leads to chest infection.

Aluminium dust treatment

Despite early positive outcomes in experimental studies of inhaled aluminium citrate powder that coats silica particles and reduces the inflammatory reaction, controlled clinical studies showed some improvement in symptoms, but no evidence of improved lung function over the longer term.[2] Moreover, side effects related to aluminium powder inhalation may outweigh potential treatment benefits.[84]

This approach has been rejected as a treatment option and no further research has been undertaken.

[k] https://herbpathy.com/Herbal-Treatment-for-Silicosis-Cid3899
[l] https://community.aafa.org/blog/aafa-explains-is-therapy-safe-and-effective-for-asthma

Polyvinyl-pyridine-N-oxide (PVNO)

PVNO, a polymer with cytoprotective qualities, showed protective effects in experimental studies and delayed fibrosis progression in one small clinical study, but this was not sustained at three years follow-up.[2]

No further research has been identified.

Thrombomodulin

While preliminary studies suggested that thrombomodulin, a protein with anti-coagulant and anti-inflammatory properties, improved survival in patients with acute exacerbation of IPF, a recent double-blind RCT showed no significant difference compared with placebo controls; and there were more serious adverse effects (e.g. bleeding) in the ART-123 group (24% vs 11% in controls).[85]

WHICH TREATMENT OPTIONS SHOULD BE ACCESSIBLE TO COMPENSATION CLAIMS?

Overall, there is no robust scientific evidence underpinning treatment options for patients diagnosed with silicosis. While there are multiple avenues of ongoing research to stop or reverse disease progression, most of it is still experimental or in very early clinical trials to determine safety and tolerability.

Therefore, the best treatment options at this time are based on a combination of the limited available evidence from relatively small studies and the expert opinions of our key informants. Table 8 summarises the first critical interventions recommended by key informants, including prudent avoidance, smoking cessation, maximising health and psychosocial support. Whole lung lavage was also recommended as a treatment option, particularly in the early stages of the disease; but our key informants had some reservations about the optimal timing for this procedure.

Table 8. Treatment/intervention options for patients diagnosed with early stage silicosis

Intervention/treatment	Type of support	Evidence
Prudent avoidance	Remove worker from silica environment to avoid further exposure • Provide support for re-employment, re-training, or compensation as required	Consensus from key informants indicated this was critical
Smoking cessation	Therapies to assist workers to stop smoking • Intensive one-on-one counselling may be required	Consensus from key informants indicated this was critical
Maximise cardiovascular and respiratory health	Exercise therapy, nutrition support and weight loss to improve physical health	Consensus from key informants indicated this was critical
Psychosocial support	Psychological counselling and psychiatric support to reduce anxiety and depression • Credible, trustworthy professionals who understand the challenges of a silicosis diagnosis	Limited evidence supported significant benefits of cognitive behavioural therapy for COPD patients Limited evidence supported enhancing social networks in silicosis patients Consensus from key informants indicated this was critical
Whole lung lavage	Surgical procedure to wash out silica from the lungs • Early stage	Limited evidence of benefits reported in studies of patients with pulmonary alveolar proteinosis and patients with moderate-severe silicosis Deemed safe and well-tolerated, with few serious side effects

Intervention/treatment	Type of support	Evidence
		Mixed views from key informants regarding use in early-stage silicosis patients • Mostly agreed it may be beneficial, but needs to be tested • Concerns about the optimal time for the procedure • Concerns about potential harms

Once patients experience symptoms and complications, other interventions may be available, including anti-inflammatory drug therapy, pulmonary rehabilitation and various treatments to manage complications (Table 9). The evidence underlying these approaches was very limited for silicosis patients; and appeared to be primarily at the discretion of the treating clinician. Lung transplant was deemed the only option for end-stage silicosis; and demonstrated significant benefits, but the number of patients was small.

Table 9. Treatment options for patients with silicosis, showing symptoms and complications

Treatment	Type of support	Evidence
Anti-inflammatory drug therapy	Supportive treatments to manage symptoms of declining respiratory function (e.g. corticosteroids)	No evidence of benefit for silicosis or IPF patients Consensus from key informants indicated no benefit
Pulmonary rehabilitation	Program of physical exercise, breathing exercises, relaxation techniques, nutritional advice	Moderate evidence of benefit for patients with COPD; limited evidence for patients with dust-related interstitial disease and silicosis Key informants indicated that pulmonary rehabilitation programs may need to be adapted for younger cohort of silicosis patients
Managing complications	Various treatments may be needed to manage exacerbations and complications of silicosis (e.g. antibiotics for infection)	Limited evidence pertaining to complications associated with silicosis Key informants agreed that exacerbations and complications required monitoring and treatment as needed
Lung transplant	Lung transplant may be needed for patients with end-stage silicosis, where no further treatment options are available	Moderate evidence of improvement in lung function; and increased median survival rates Key informants agreed that lung transplant was the last option for end-stage silicosis; but the timing was important to avoid the challenges

Treatment	Type of support	Evidence
		associated with severe stiffening of the lungs

Several promising treatment options have emerged from the research literature (Table 10). The treatment that is potentially closest to being realised for silicosis patients is antifibrotic drug therapy, which is progressing through clinical trials. Cell-based therapies are also a promising avenue, but are at an earlier stage of the research investigation process; and are unlikely to be available for clinical use in the near future. All other approaches are still experimental or just entering safety and tolerability trials.

Table 10. Emerging promising treatment options for silicosis

Treatment	Details	Evidence
Anti-fibrotic drug therapy	Nintedanib and Pirfenidone have been approved for treatment of IPF A clinical trial is underway for silicosis	Nintedanib and Pirfenidone have demonstrated in IPF clinical trials that they slow the decline in lung function; are safe and well-tolerated; with mild gastro-intestinal side effects Not yet approved for use in silicosis patients Key informants supported the use of antifibrotic drugs for treatment of silicosis
Cell-based therapies	Inhaled or injected mesenchymal stem cell therapy to reduce fibrosis and slow disease progression	Experimental evidence in animal models of silicosis has demonstrated reduced inflammation and fibrosis Early clinical trials have shown good safety and tolerability This approach is promising, but larger, controlled trials are needed
Antibiotic drug therapy	Prophylactic doses of antibiotics to prevent multiple infections, which is common in patients with IPF and other chronic lung conditions	Limited evidence that azithromycin (AZT) reduced the rate of infection and use of health services in patients with IPF This approach is promising for managing complications, but larger, controlled trials are needed
Immunomodulation	Boosting patients' immune system to prevent complications related to silicosis	Limited evidence has shown preliminary benefits of thymalfasin treatment RVT-1601 sodium cromoglycate trial is currently underway
Herbal treatment	Tetrandrine is a herbal medicine to reduce fibrosis in the lungs	Limited evidence from experimental studies and one controlled study with silicosis patients has demonstrated

Treatment	Details	Evidence
		improved lung function Appropriate clinical trials are needed

SUMMARY AND IMPLICATIONS

Although the main focus of this Environmental Scan was to review the current and emerging treatment options for silica-related diseases, the experts strongly emphasised three areas that provide context for current treatment as well as strategies for developing future treatments. These areas were: prevention; early detection and accurate prognosis; and a need for adequate research funding.

Prevention

Reducing the risk of exposure to silica through the hierarchy of controls, appropriate standards, health monitoring and education is the **only** known way to reduce the incidence of silicosis and its impact on workers' health.

Diagnosis and prognosis

Early detection is enabled through the health screening program for stoneworkers. Although a silicosis diagnosis implies a life-shortening disease, there are uncertainties about the extent and rate at which the disease is likely to progress if detected early. This may impact on strategies to manage workers' physical health, mental health and future employment prospects. Importantly, while early detection is essential for stone-workers, workers in other industries that use materials containing silica may also be at risk.

Monitoring disease progress is important to detect changes over time and adjust treatments accordingly.

Early management and administrative actions

After a positive diagnosis is made, the first, and most important, action is to remove the worker from the risk of further exposure – i.e. prudent avoidance. Our key informants acknowledged that this is challenging for many workers who prefer to return to their well-paid jobs and may resist transferring or re-training in a different industry.

There are many challenges associated with medico-legal issues around compensation. These include the poorly characterised use of progressive massive fibrosis as a marker of compensation; and the tension between clinicians desire to provide optimal treatment and disease management and lawyers' efforts to obtain compensation for their clients.

Early intervention and support

The most important interventions highlighted by key informants were: Smoking cessation; maximising cardiovascular and respiratory health; and providing psychosocial support for silicosis patients.

Whole lung lavage to reduce the silica load in patients' lungs was supported by limited evidence for silicosis patients. However, there were mixed views amongst the key informants. Most key informants agreed it was a safe procedure that could potentially slow the rate of disease progression in young, asymptomatic patients. However, some key informants raised concerns about the optimal timing of the procedure and the potential for side effects. Overall, it needs to be monitored to determine long-term benefits and observe adverse effects, as this is currently unknown in the cohort of young stoneworkers.

Mid-stage treatment and symptom management

No current treatments for silica-related disease effectively reverse lung damage. While managing symptoms of silicosis requires an individual approach, depending on specific exacerbations and complications, there was no evidence to support the use of anti-inflammatory medications, such as corticosteroids. Current pulmonary rehabilitation programs have beneficial effects for patients with

various lung diseases (e.g. COPD), but require ongoing support; and may need to be modified to engage younger cohorts with early stage silicosis.

Late-stage treatment of silicosis

Lung transplant is the only option available for patients with severe fibrosis and lung dysfunction. However, key informants cautioned against waiting too long before referring patients for this option, as the surgery is substantially more difficult in very severe cases. In addition, this option is limited by the availability of donor lungs and the requirement that patients have quit smoking.

Emerging treatment options

Our understanding of the pathophysiology of silicosis is increasing and the investigations into mechanisms have highlighted several targets in the disease pathway for future research and treatment options. The most promising emerging treatment options are the antifibrotic drug therapies (Pirfenidone and Nintedanib), which have demonstrated safety and positive effects in clinical trials for IPF. In general, our key informants agreed that this option was the closest to being ready for treating silicosis patients. However, there were still some challenges to address, including determining how early in the disease process patients should be prescribed antifibrotic therapy.

> *In those more obvious cases that are progressing then yes, you go, "Let's look at the antifibrotics and whatever else we can throw at them." But if we're not talking about the same condition and we're not diagnosing them in a similar manner, or at the same stage, then we're not even speaking the same language. Key informant #3*

The next promising avenue for treatment is cell-based therapy (e.g. mesenchymal stem cells). However, this approach still needs substantial investment in clinical trials to determine safety, tolerability, dosage, route of administration and other parameters (e.g. co-administration of growth factors or cytokines).

Beyond antifibrotics and cell-based therapies, other potential treatments are still in early stages of experimental studies or clinical trials for safety (e.g. antibiotic drug therapy, immunomodulation, tetrandrine).

Finally, other future treatment approaches are still at a conceptual stage. However, new technology, such as single cell RNA sequencing, may provide a feasible pathway to accelerate drug discovery for silicosis treatment.

Key informants agreed that there is an urgent need for funding to investigate novel targets for drug therapy or to leverage on the known effects of existing drugs for diseases that follow a similar course (e.g. IPF).

> *Although we haven't made bad decisions, or wrong decisions that we're going to regret, I think we're at a point where if we continue to do nothing, and we don't take anything away with regards to further research in the area, then we haven't done enough. - Key informant #3*

Implications

At this time, silicosis treatment options are part of a moving landscape as advances in research and practice adapts to the changes in knowledge. Prevention, early detection and accurate diagnosis are critical for all workers at risk of silica exposure, irrespective of the industry. Removing workers from further exposure is the essential first step after diagnosis and this has major psychological and financial implications for workers' wellbeing. Therefore, understanding the disease course after

workers are removed from exposure is critical to determining their treatment options and relies on regular monitoring.

While the current array of silicosis treatment options is limited primarily to managing symptoms and complications, clinicians are poised to take advantage of various advances in research knowledge and technologies. Ultimately, their success will depend on the availability of adequate funding to expedite appropriate investigation in this area.

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APPENDIX

Table 11. Details of spirometry measures

Outcome measure	Details
FEF_{50}	Forced expiratory flow: average flow rate at 50% of the volume of exhaled air, expressed as the average rate at which air is exhaled when 50% remains in the lung
FEV_1	Forced expiratory volume during the first second: volume of air exhaled during the first second of forced exhalation, expressed as a percentage of predicted value
FVC	Forced vital capacity: volume of air that can be forcibly exhaled from the lungs after a maximum inhalation, expressed as a percentage
FEV_1/FVC	Proportion of a person's vital capacity that they can exhale in the first second of a forced expiration to the full vital capacity, expressed as a percentage (normal values are approximately 75%)
PEF	Peak expiratory flow: maximum speed of expiration, expressed as litres per minute (L/min)
VC	Vital capacity: Maximum volume of air a person can exhale after a maximum inhalation, expressed as a percentage