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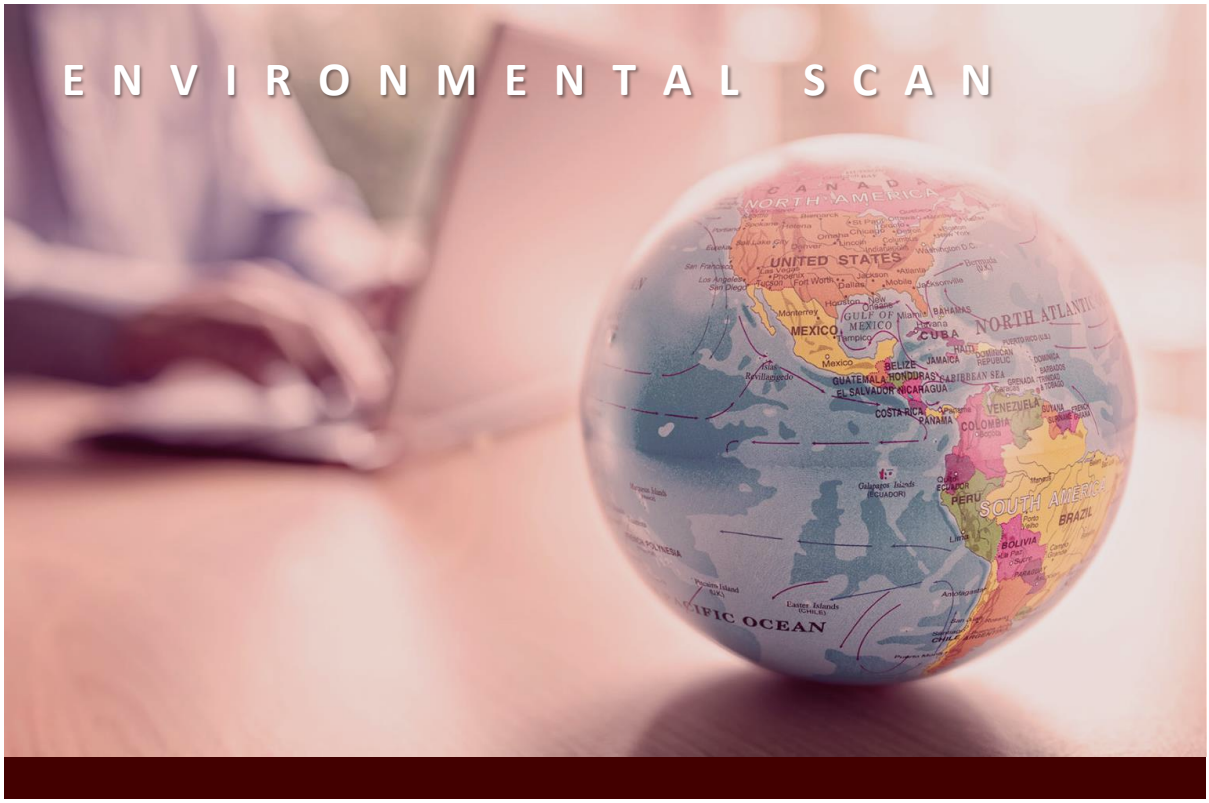

Silica exposure-related disease

Current and emerging treatment options: Update

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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Acknowledgments

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Disclaimer

Please note: This Environmental Scan has been produced by the Institute for Safety, Compensation and Recovery Research (ISCRR) in response to specific questions from WorkSafe Victoria. The content of this report does not involve an exhaustive analysis of all existing evidence in the relevant field, nor does it provide definitive answers to the issues it addresses. The findings were current at the time of publication, April 2022. Significant new research evidence may become available at any time. ISCRR is a joint initiative of WorkSafe Victoria and Monash University. The opinions, findings and conclusions expressed in this publication are those of the authors and not necessarily those of WorkSafe Victoria or ISCRR.

EXECUTIVE SUMMARY

Background

Workers who are exposed to high levels of respirable crystalline silica dust are at risk of developing silica-related diseases, such as silicosis. Since identifying a number of cases of silicosis amongst workers in the artificial stone benchtop industry, WorkSafe Victoria has invested in research to identify optimal treatment and management strategies for workers at risk of silica-related disease.

Purpose

In 2020, the Institute for Safety, Compensation and Recovery Research (ISCRR) undertook an Environmental Scan for WorkSafe Victoria to identify the treatment options for occupationally-acquired silica-related disease. This report provides an update to the previous work and focuses on the current and emerging treatments for silica-related diseases and associated complications.

The key research questions were:

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

Approach

The Environmental Scan comprised two approaches:

1. Worldwide desktop scan: searches comprised publicly available online resources, including peer-reviewed articles published between January 2020 and January 2022; and national and international guidelines.
2. Key informant interviews: seven interviews were undertaken with clinical experts in silica-related diseases.

Key findings

Since the previous Environmental Scan published in 2020, several strategies have been implemented to reduce the risk of exposure to silica dust in the workplace. These include: licensing artificial stone manufacturing businesses in Victoria; a ban on dry cutting; and reduced exposure limits. Screening and health surveillance have also been implemented for early identification of silica-related diseases and to monitor disease progression over time.

In terms of management and treatment options, very little has changed since the previous report and there are no proven treatments to reverse or halt the disease process once it has started. Clinical experts emphasised the importance of removing workers from further silica dust exposure if they are diagnosed with silicosis; and providing immediate and ongoing psychological support to help them through the challenges of diagnosis and losing their job. Smoking cessation support and managing symptoms as they occur are essential for all patients with a positive diagnosis.

In cases where patients show signs of particulate matter in the lungs, whole lung lavage may be considered. However, if the disease has progressed to lung fibrosis, anti-fibrotic medication (nintedanib) may soon be available through the Pharmaceutical Benefits Scheme. Once fibrosis is advanced, the only remaining option for patients is a lung transplant, if they are eligible.

Although there is a wide range of pharmacological agents currently under investigation, most are still in early stages of determining safety and efficacy or still in experimental studies. Therefore, it is likely to be many years before new proven treatment options become available.

Insights and implications

The only effective strategy for managing silica-related disease is to protect workers from silica dust exposure. Where exposure is inevitable, early identification through screening and monitoring may slow disease progression, but even when workers are no longer exposed, longer-term outcomes are still unknown.

Given the variability in disease symptoms and complications, management and treatment require a very individual, tailored approach. For example, a multidisciplinary team may be needed to treat silica-related complications such as scleroderma, systemic lupus erythematosus, rheumatoid arthritis and other autoimmune disorders.

Beyond treating the physical symptoms, a high level of support is needed for managing psychological consequences and assistance in seeking a rewarding job in an alternative industry.

Over the longer term, it may be necessary to monitor workers who have left the industry, but are still at risk of developing silica-related conditions, such as lung cancers; and to screen workers in other industries where high levels of respirable crystalline silica continue to put them at risk.

In conclusion, a two-pronged approach is needed to manage both the risks and the consequences of exposure to silica in the workplace. This includes a strong regulatory system to protect workers' health and welfare; and efficient health surveillance for early identification of silica-related disease. Current management of occupationally-acquired silica-related disease is limited; and, while there are some promising treatments under investigation, none will be available in the near future. Therefore, the current cohort of workers with silica-related conditions require an individually tailored approach involving matching the right therapy to the patient who is most likely to benefit.

INTRODUCTION

In May 2020, the Institute for Safety, Compensation and Recovery Research (ISCRR) undertook an Environmental Scan for WorkSafe Victoria (WSV) to identify treatment options for occupationally-acquired crystalline silica exposure-related disease.

Since then, WSV has funded a program of work, including:

- Screening Registry, which collects data on workers in the artificial stone industry
- Disease Registry, which collects data on all silica-related diseases in workers in Victoria
- Analyses of health data from screened workers.

Recognising the importance of preventive strategies to protect workers in the artificial stone industry, there have been changes in workplace safety policies, including:

- Ban on dry-cutting
- Licensing of artificial stone businesses
- Reduction in silica dust environmental exposure standard (to 0.05mg/m^3) and enhanced ventilation requirements
- Increased use of respiratory personal protection equipment for workers
- Regular screening of workers for early identification of silica-related health conditions.

Although these improvements will benefit the next cohort of workers in the industry, there has been an increase in the number of current workers diagnosed with silicosis and other autoimmune disorders associated with exposure to silica.

WSV requested ISCRR to provide an update on treatment and recovery options for workers with occupationally-acquired crystalline silica diseases and associated complications.

Background

To avoid duplication of effort, the current updated review should be read in conjunction with the earlier report,[1] which provides more detail on different forms of silicosis and addressed prevention strategies and screening criteria.

Silica and silica-related disease

A growing number of industries in which workers may be exposed to silica has been identified (Table 1).[2] The risks associated with exposure vary across the specific tasks and industries.

Chronic silicosis typically develops in workers exposed to low concentrations of respirable crystalline silica over a prolonged period (20-30 years).[2] However, growing numbers of workers in the artificial stone industry are showing signs of an accelerated type of silicosis, which develops within three to five years due to exposure to high concentrations of silica.[3] This also means that they are a younger cohort (25-35 years) when diagnosed compared with other industries; and the incidence of silicosis is at least five times higher in artificial stone workers (~32%) compared with miners (~6%).

In Australia, other key sources of exposure include construction, tunnelling, mining and some farming. With the exception of tunnellers in Sydney, who have high silica exposure working with sandstone, workers in mining, quarry work or tunnelling develop a chronic type of silicosis over 15 to 20 years and are aged in their forties or fifties when diagnosed.

There're tunnellers in Sydney – and it will be less the case in Melbourne, but probably there's some instances. But Sydney's built on sandstone, so a lot of the tunnelling is going through sandstone, which is almost 100% quartz. So, there's very high levels if the exposures aren't controlled. And often they're not well controlled. - Participant #3

It's the total dose, it's not just the intensity. The intensity is a problem, especially if it's really horribly high, but otherwise it's the total amount. And so people working in construction, particularly in demolition, but also in other areas of construction, there's a lot of people – like concreters – a lot of people get exposure to silica and they get it every day. - Participant #3

The exposures are not well controlled, not much point having a standard if the standard isn't adhered to. … Even if they are measured, the person in charge of them might have said, "Well, that's not a typical measurement, come back and measure it again another day." Or, "That task isn't being done anymore, so we don't need to worry about it." - Participant #3

Table 1. Industries, tasks and source material where workers may be exposed to respirable crystalline silica

Industry/ Occupation	Specific task/ Operation	Source material
Abrasive blasting	Rust and paint removal, automotive repairs	Sand, sandstone, abrasives
Agriculture, farming	Mechanised ploughing, harvesting	Soil
Cement and brick manufacturing	Raw material processing	Clay, sand, limestone
Chine, ceramic and pottery manufacturing	Mixing, moulding, glaze or enamel spraying, sculpting	Clay, shale, flint, sand, quartzite
Construction	Bricklaying, concrete cutting, paving, cement finishing, laboring, abrasive blasting, demolition, earthworks	Sand, concrete, rock, soil, plaster
Denim jean production	Sandblasting	Sand, abrasives
Dental material manufacturing	Abrasive blasting, polishing	Sand, abrasives
Excavation	Earthmoving, drilling, digging	Soil, rocks
Glass, fibreglass manufacturing	Raw material processing	Sand, quartz
Hydraulic fracking	Drilling, fracking operation	Rock, sand
Iron, steel mills, foundry	Foundry casting production, furnace installation and repair	Sand, refractory materials
Jewellery production and cleaning	Cutting, grinding, polishing gems	Semiprecious stones or gems, abrasives, glass
Mining and related milling	Most occupations (above and underground mining), rock drilling	Ore, associated rocks

Industry/ Occupation	Specific task/ Operation	Source material
Ornamental stone and tombstone repair	Stonemasonry, sandblasting	Sandstone, granite, sand
Paint manufacturing	Raw material handling	Fillers (Tripoli, diatomaceous earth, silica flour)
Quarrying and related milling	Crushing rock, sand and gravel processing	Sandstone, granite, gravel, slate
Road/highway construction and repair	Sawing, breaking and grinding road materials	Concrete, asphalt, bitumen
Sand quarrying and processing	Silica flour production	Sand, silica flour
Shipbuilding and repair	Abrasive blasting	Sand, abrasives
Soap and cosmetic production	Manufacturing or occupational use of abrasive soaps and souring powders	Silica flour
Stone benchtop fabrication and installation	Cutting, grinding, polishing	Artificial stone, sandstone, granite, porcelain
Tuckpointing	Mortar removal, grinding	Bricks, mortar
Tunnelling	Blasting, drilling	Soil, rock, sandstone
Waste incineration	Maintenance, cleaning	Fly ash

Source: Hoy and Chambers (2020)[2]

The pathogenesis of silicosis is complex and not completely understood.[4] Silica has a direct cytotoxic effect on macrophages, which respond to inflammation and are responsible for clearing debris from lung tissue. Contact with silica particles inhibits the macrophage function, setting off a cascade of reactions and leading to inflammation, autoimmune responses and eventually, lung fibrosis.

Key aspects of silica-related disease

- There are different types of silicosis
- Patients may be positive for silicosis, but asymptomatic
- Early clinical signs are similar:
  - Dyspnoea (shortness of breath or laboured breathing)
  - Chronic cough
  - Respiratory dysfunction
- Symptoms may progress and/or develop complications
  - Silicotic nodules fuse to form masses (>1cm) – progressive massive fibrosis (PMF)
  - Development of central cavitation (an abnormal thick-walled, air-filled space in the lung) and increased risk of mycobacterial infection
  - Enlarged hilar or mediastinal lymphadenopathy (swelling in lymph nodes) – respiratory problems, including coughing, wheezing and airway obstruction
  - Pleural thickening: chest pain and breathing difficulties
  - Increased risk of spontaneous pneumothorax (collapsed lung)

Health screening of workers in the artificial stone benchtop industry has identified 36 per cent of screened workers (86/239) with silicosis.[5] Moreover, approximately 37 per cent of those with silicosis had biomarkers suggesting there was potential for developing autoimmune disease.

As reported previously,[1] no curative treatment has been identified and the only known effective strategy is prevention – avoid exposure altogether or, at the very least, limit exposure through the best possible engineering controls. Early screening is also essential to identify early stage disease and avoid continued exposure before fibrosis is established.

OBJECTIVES

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

Research questions

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

METHOD

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, guidelines and government reports
2. Key informant interviews: Insights, experiences and current clinical practices from clinical 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 2020 to January 2022. The search strategy involved a combination of the following terms: 'silica' OR 'silicosis' OR 'pulmonary fibrosis'; 'scleroderma' OR 'systemic lupus' OR 'Raynaud' OR 'rheumatoid arthritis' OR 'lung cancer'; and 'treatment' OR 'intervention' OR 'recovery' OR 'rehabilitation'.

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

Table 2. Inclusion and exclusion criteria for the literature review

	Inclusions	Exclusions
Patient / population	Workers who have acquired any type of crystalline silica disease in the course of their work, including chronic, complicated or accelerated silicosis, pulmonary massive fibrosis, lung cancer, scleroderma or other autoimmune diseases associated with silica exposure (e.g. Raynaud's syndrome, systemic lupus erythematosus, rheumatoid arthritis)	Workers who developed the aforementioned disorders in other settings, not related to occupational silica exposure; workers exposed to other hazardous materials that develop illnesses with a different pathogenesis; workers with psychological illness not specifically related to the above conditions
Intervention / indicator	Any treatment or intervention that reduces or manages the physical, emotional and psychosocial effects of silica exposure	Pre-clinical studies (e.g. *in vitro* or animal studies)
Comparison / control	Standard care or no comparator	None
Outcomes	Improvements in physical symptoms (e.g. respiratory function), psychological wellbeing and quality of life; 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 disorders	Opinions, letters, editorials, qualitative studies or articles that do not address treatment options
Publication details	Peer-reviewed publications; grey literature	None
Time period	Articles published since January 2020	Articles published before 2020

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. No quality assessment was conducted for the studies included in this review.

Key informants

Key informants were invited to provide insights on the current status of treatment options in the field; and to discuss new or emerging options that may be promising. Potential interviewees, including those who had contributed to the previous Environmental Scan,[1] were contacted by email, inviting them to participate and arranging a suitable time for a phone interview. Table 3 lists the participants. Interviews were recorded and transcribed; and key themes were extracted and reported in a qualitative synthesis.

Table 3. List of key informants who participated in interviews

Name	Affiliation
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 Nicole Goh	Respiratory physician, Alfred Hospital
Dr Ryan Hoy	Senior Research Fellow, Occupational and Environmental Health Sciences, Alfred Hospital, Victoria
Dr Abe Rubinfeld	Melbourne Lung and Sleep specialist, Royal Melbourne Hospital

FINDINGS

The most important thing that WorkSafe can do is to stop people being exposed.
- Participant #3

The two cornerstone strategies for managing the risks associated with occupationally-acquired silica-related disease are:

1. Regulating exposure to silica, including monitoring adherence and effectiveness of controls
2. Health screening to identify early evidence of disease, especially in those who are asymptomatic. Early detection is critical for reducing morbidity and preserving lung function in those who have been exposed to silica.

The previous ISCRR report provided details on prevention, diagnosis, prognosis and early management strategies as well as treatment options.[1] While the current report focuses on treatment, there are some updates in prevention and diagnosis that are worth mentioning:

Prevention

- A new national Code of Practice has been developed to manage the risks associated with silica in the engineered stone industry[6]
- New regulations have been introduced in Victoria for engineered stone workplaces, including mandatory licensing and prohibition on dry-cutting[7]

Diagnosis and prognosis

- Screening Registry, which collects data on workers in the stonemason industry has been established in Victoria and Queensland[8]
- Disease Registry, which collects data on all silica-related diseases in workers in Victoria[8]
- Health data from screened workers in Victoria are analysed to monitor disease progression[9]
- Investment in silicosis research through the Medical Research Futures Fund. For example, the SHIELD study aims to identify biomarkers in lung fluid and tissue from engineered stone workers to understand disease pathogenesis, progression and risk factors. This approach may facilitate more accurate diagnosis and disease staging as well as identify off-label use of existing drugs or guide development of new potential targets for treatment.[10]

CURRENT GUIDELINES AND POSITION STATEMENTS

Although clinical practice guidelines for treating and managing silica-related diseases were not identified, three documents may be useful for guiding decisions about managing risks related to silica exposure and clinical treatment of silica-related disease.

Silicosis

In February 2022, the Commonwealth Department of Health released ***The National Guidance for doctors assessing workers exposed to respirable crystalline silica dust with specific reference to the occupational respiratory diseases associated with engineered stone***.[11] This comprehensive document was developed by a group of medical experts from various fields, including respiratory and thoracic medicine, occupational and environmental medicine and workplace health and safety. It has been endorsed by several relevant clinical colleges, including Thoracic Society of Australia and New Zealand, the Royal Australian College of Physicians, the Australian College of Rural and Remote Medicine and the Royal Australian and New Zealand College of Radiologists. The document provides guidance to health care professionals to identify and assess workers with silica-related conditions and to monitor disease progression. A summary of the key recommendations for case identification and health surveillance are available in a summary document on the Department of Health website.

In brief, the recommendations include:

- Referral to relevant specialist care – e.g. respiratory physician
- Lung function testing – e.g. spirometry
- Radiological investigations – e.g. chest computed tomography
- Other tests – e.g. autoimmune screening
- Psychosocial support
- Patient education – e.g. smoking cessation
- Ongoing health surveillance.

The Thoracic Society of Australia and New Zealand published a position statement to promote the awareness of artificial stone silicosis and associated lung disease; and to highlight the optimal surveillance strategies needed to identify workers at risk.[12] The focus of this position statement was to emphasise the need for routine surveillance. No recommendations on disease management were provided.

Interstitial lung diseases - general

The Indian Chest Society and National College of Chest Physicians in India used evidence from a systematic review of the published research and a working group of experts to develop clinical practice guidelines for interstitial lung disease, a broad group of lung diseases that includes silicosis.[13]

In addition to recommendations related to accurate diagnosis, avoiding continued exposure and inhalation of tobacco products, the following treatment and management strategies are:

- Pulmonary rehabilitation in patients with dyspnoea (shortness of breath or laboured breathing)
- Annual influenza and pneumococcal vaccinations
- Treatment for underlying lung disease and supplemental oxygen for patients with hypoxemia
- Consider non-invasive ventilation (e.g. via face mask, rather than endotracheal airway) as early as possible for patients needing high-flow supplemental oxygen at rest
- Mechanical ventilation in patients with acute exacerbation of disease with respiratory failure should be considered with caution – after appropriate counselling
- Monitoring disease with spirometry is recommended at 4-6-month intervals
- Lung transplantation is the only treatment option for patients with advanced disease
- Palliative care is required for all patients with advanced disease
- Oral corticosteroids for 4-12 weeks are appropriate for patients with acute hypersensitivity pneumonitis or associated rheumatoid arthritis. Low-dose oral corticosteroids may be considered for scleroderma. High doses are associated with renal crisis
- Cyclophosphamide or mycophenolate mofetil treatment may be considered for patients with scleroderma.

Idiopathic pulmonary fibrosis

An international consortium of thoracic and respiratory societies in the US, Europe, Japan and Latin America developed clinical practice guidelines for idiopathic pulmonary fibrosis (IPF). IPF, which is a chronic progressive interstitial lung disease characterised by lung fibrosis, shares several clinical features and symptomology with silica-related diseases.[14]

While there are differences, treatment/management strategies in the early stages are similar, including:

- Improving symptoms (e.g. cough, dyspnoea)
- Improving overall health status
- Preserving lung function
- Maintaining adequate oxygenation
- Minimising adverse effects of therapy
- Reducing the frequency of exacerbations
- Improving survival.

Table 4 lists the medications that have been used to treat IPF and the current recommendations pertaining to their use. Antifibrotic agents (nintedanib, pirfenidone) have been extensively investigated for IPF and are the only drugs currently accepted for use in the recent guidelines for the treatment of IPF. Data from several trials (e.g. INPULSIS, ASCEND, CAPACITY) demonstrated a significant slowing in the rate of decline of forced vital capacity (FVC) compared with placebo. Typically, FVC is used as a proxy measure of disease progression. The most common adverse effects were diarrhoea and nausea; and at least 30 per cent of patients on nintedanib experienced a serious adverse event (e.g. liver injury, gastrointestinal disorder/perforation, bleeding event, or

cardiovascular event). Use of anti-fibrotic medications for treating silicosis is discussed below on page 25.

Corticosteroids are used widely for acute exacerbations over the short term, but evidence does not support longer-term use.

Table 4. Guideline recommendations for treating IPF

Agent	Recommendations	Strength/quality of evidence
Nintedanib, antifibrotic	For use	Weak/Moderate
Pirfenidone, antifibrotic	For use	Weak/Moderate
Nintedanib + pirfenidone	Uncertain	Insufficient evidence
Imatinib, chemotherapy	Against use	Strong/Moderate
N-acetylcysteine + pirfenidone	Against use; possible option in minority of patients	Weak/Low
N-acetylcysteine monotherapy	Against use	Weak/Low
Corticosteroid monotherapy	Against use	Strong/very low
Combination prednisone + azathioprine + N-acetylcysteine	Against use	Strong/Low
Sildenafil, phosphodiesterase-5 inhibitor	Against use	Insufficient evidence
Endothelin receptor antagonists (ambrisentan, macitentan, bosentan)	Against use	Insufficient evidence

Source: Glassberg (2019)[14]

CURRENT TREATMENT OPTIONS

In early days, at the moment, I don't think there is a lot you can do in terms of actual proven remedies for the process. In late stage, you obviously refer them on for a transplant. - Participant #2

Current treatment options for patients with established silicosis are limited as there is **no effective treatment** to reverse or halt disease progression.[15] While there has been a lot of research activity over the past two years, no new proven treatment options have been identified since the earlier review.[1]

In the absence of a cure, the key aims are to manage symptoms and complications, preserve lung function and slow disease progression, if possible. To do this, clinicians still need to make decisions about who to treat, when to treat and how to treat patients.

One of the many challenges of treating silica-related conditions is the variability in the course of the disease and involvement of multiple organ systems. Current knowledge suggests that exposure to silica triggers both an inflammatory and an immunological response that contribute to the development of fibrosis.[4] However, while progressive fibrosis is a common characteristic, not all patients demonstrate inflammatory and immunological responses. Therefore, accurate diagnosis and assessment of symptoms is essential for each individual, as there are potential side effects associated with some medications.

Difficulty is with most anti-inflammatory approaches, they're using drugs that are potent, have potentially serious side effects on the body's immune system and susceptibility to infections and things like that, so it's not something that you'd go into lightly. - Participant #2

Once a diagnosis has been confirmed, current treatment options are limited, but vary depending on the stage or severity of the condition. For all confirmed cases, the essential first steps are:[15]

1. Stop exposure

Remove workers from the workplace to avoid further exposure. This may be sufficient for those who are asymptomatic or at a very early stage, with no evidence of lung dysfunction. However, there are conflicting views about disease progression after exposure has ceased. Some research suggests that removing artificial stone workers from further exposure to silica may not be enough to stop disease progression.[16] For example, a cohort of 106 artificial stone workers were diagnosed with silicosis in Spain. Despite ceasing work in the stone industry, 56 per cent showed disease progression at 4-6 years follow-up (e.g. decreased lung function); and the number with progressive massive fibrosis increased from seven to 40 (almost sixfold increase). It is not clear whether the disease is destined to progress, albeit more slowly, even after exposure ceases; or whether the lung function of a person exposed to silica declines more rapidly than lung function of an unexposed individual. The general consensus is that removal from the silica environment is essential.

Just from identifying that there's a problem at an early stage and removing them from that exposure has meant that their disease has stabilised quite nicely. - Participant #1

If somebody is exposed and they develop silicosis, it doesn't matter what you do, that silicosis will advance. Now, how quickly it advances and the extent of that advance – I think a lot of the time, we don't know what the determinants of that are, apart from more dust. - Participant #3

The appropriate response is to remove the person from the environment. But that won't overcome the effect of the initial exposure. But most of the time it will be many years, decades, before people have a problem. - Participant #3

Even if the disease doesn't advance much, they might still get symptoms a lot earlier than other people just because it [lung function] got down to that level earlier. But they wouldn't have noticed anything really until it got to that level. - Participant #3

2. **Smoking cessation**

Encouraging and supporting patients to stop smoking is necessary for their overall respiratory and cardiovascular health. It is also essential in late-stage disease to maximise their chances of obtaining a lung transplant, if needed.

Smoking rates in this group are higher than the background rate in the general population even adjusted for age and gender. So, we've got a good link with the smoke-free program at the Alfred and that's a program that's run by the pharmacy departments. There's very few … smoking cessation services around, but to actually have one that we can refer directly to when they see a specialist in this area, has been really beneficial. - Participant #7

Instead of the usual -

"Here's the number for Quitline and please give them a call." We talk about nicotine replacement and these sorts of things, but actually getting them to follow it up with a smoking cessation expert's been really helpful. - Participant #7

3. **Vaccination**

Regular vaccinations against pneumonia and influenza are recommended. Given the effect of COVID-19 on respiratory health, vaccinations against COVID-19 are also recommended.

4. **Health surveillance**

Routine health monitoring is essential to assess disease progression and determine whether, when and what type of treatment is required.

Everyone should be followed at least six monthly or yearly if it's early and not particularly progressive, possibly indefinitely but certainly for five to 10 years. - Participant #2

Leaving the industry is not an easy option for workers.

I have one man that still is in the industry, because he bought over the stonemason industry and he has no other skills, so he's chosen to continue working in the industry. He tells me he's got full PPE on. So, obviously you can advise on avoidance but at the end of the day these men usually they would have left school and that's the only thing they've known and they've got families to support. - Participant #6

Outcome measures

Table 5 lists the most common measures to assess respiratory function and disease progression in patients with silica-related diseases and complications (e.g. scleroderma). These outcome measures are not always accurate for measuring disease progression and others, such as antibody testing for silica-related autoimmune disorders, are expensive (Participant comment). Therefore, there has been growing interest in development of less invasive and more cost-effective biomarkers to monitor disease progress.[17] The Australian SHIELD study aims to contribute to the knowledge in this area (see page 32 for more details).

Table 5. Common outcome measures of silica-related disease and associated complications

Outcome measure	Details
Forced vital capacity (FVC)	The maximum capacity of air that a patient can exhale in a spirometer after a maximum inspiration. It is reported as the percentage of the predicted value for the patient. FVC of ≥10% relative decline is used to measure progressive lung dysfunction
Carbon monoxide diffusion (DLCO) test	Measures the ability of the lungs to transfer gas from inhaled air to the red blood cells in pulmonary capillaries. It is reported as the percentage of the predicted value for the patient. Low DLCO (≤ 50% predicted) may indicate hypoxemia due to scarring that restricts gas exchange
High resolution computed tomography (HRCT)	Shows computerised body images based on transversal cuts using x-rays. The diagnostic image is taken using tomography and reconstructed digitally. HRCT is a measure of interstitial lung disease, including extent of fibrosis and ground glass opacity
Modified Rodnan Skin Score (mRSS)	A measure of skin thickness, which correlate with severity of skin fibrosis (0= normal to 51 = severe thickening in 17 areas of the body)[18]; limitations include high inter-observer variation and poor sensitivity to change

Source: Flórez-Suárez et al. (2020)[17]

The treatment options for patients who show signs of disease progression are limited and each patient's individual and disease characteristics need to be carefully considered in selecting the appropriate treatment pathway. Treatment options fall broadly into four categories, depending on the stage of their disease:

1. **'Wait and see'**: for workers who are asymptomatic, or show mild symptoms, management of symptoms as they arise may be sufficient for months or years
2. **Whole lung lavage**: for patients in early stage silicosis, with ground glass abnormality identified, but without established lung fibrosis (see page 23 for more details)
3. **Anti-fibrotic drugs (nintedanib)**: for patients with early signs of fibrosis (see page 25 for more details)
4. **Lung transplant**: for patients with more advance disease, such as progressive massive fibrosis.

Management of symptoms

Given the variability in symptoms and complications across the course of progressive lung diseases, there is a need to manage symptoms as they occur. Two critical aspects are managing the psychological distress associated with a positive diagnosis and maximising cardiovascular and respiratory function.

Psychological support

Although psychological support was discussed in detail in the previous report,[1] it was highlighted again by all the experts in this review. In brief, they emphasised the importance of addressing the psychological sequelae of a positive diagnosis; and how it impacted on all areas of workers' lives, including their physical health (e.g. weight gain, substance use), wellbeing (e.g. anxiety, depression), relationships, return-to-work prospects and various aspects of their compensation cases.

> *The psychological impact of the diagnosis has been quite profound. Within the first five years, considering that the vast majority of these diagnosed workers are not going to have physical decline of significance, at least in my experience, the most important thing to address is the psychosocial aspect of it. The relationship breakdowns in this cohort are substantial. - Participant #5*

> *Adjustment disorder has been almost inevitable I think in most of these workers, depression, anxiety, you see that a lot, a background of often, drug misuse as well so all of those things come into play so definitely, psychological support through that [early] period. - Participant #1*

> *These are guys that have had an adjustment and they're grieving the loss of their employment and the life that they thought that they had. The meaning in their life has been stripped away. Even though they might only be 32, they were the leading hand in their workshop and people came to them for advice regularly, and if there was a problem, they were the person that would solve it. All of a sudden, there's really no one coming to them for advice, they're not really helping anyone, they're not really doing anything. They're finding that it's difficult to get employment in other areas, particularly when you've been labelled as having this diagnosis. - Participant #5*

The effectiveness of psychological support varies across individual's experiences.

> *I think for someone who's had a good income, who sees being a stonemason as they usually do, as a good, long-term career path which has suddenly been taken away from them, psychological supports have really been of limited effectiveness because they can't go back to doing what they'd like to do, a job that they actually enjoyed doing and were well compensated and all of a sudden, their future and their future health is totally uncertain because they have all heard about the potential for progression, incurability. It's been a catastrophe for mostly young workers. - Participant #2*

Two key challenges are patients' willingness to seek psychological support and, if they agree, getting access to mental health professionals within a reasonable timeframe.

> *Most patients actually did not take up on it. Most patients go, "No, no I'm fine." So, these are young stoic men, so I haven't had anyone that had taken up the offer for psychologist. … I think the resources are there but whether they take it up is a different question. - Participant #6*

> *There's an absolute shortage of both psychiatrists and psychologists. The experience locally has been that they haven't really had a lot of assistance at all. I think they're a difficult sort of group to work with anyway, so they probably really need someone that has an interest in this sort of area and is willing to work with them quite closely. - Participant #5*

Linking to worker's general practitioner may be beneficial for identifying the most suitable mental health practitioner for the individual.

> *What we usually do is link the GP back into that discussion because our patients are from all around Melbourne, around Victoria really, so the GP's going to have a better idea as to who's a good psychologist who would be appropriate for that individual in their area. So, we do have to typically put it back on the GP to arrange that. - Participant #7*

Maximising cardiovascular and respiratory function

Maximising cardiovascular and respiratory health was discussed in the previous report and is still considered a good strategy for patients with dust-related respiratory diseases to improve overall health and quality of life in the short-term.[1]

The most common approaches involve management of respiratory symptoms, such as breathlessness and persistent cough in the early disease stages; and declining lung function at the later stages.

Inhalers may be needed to provide rapid relief for breathlessness by opening up airways.

> *There are some forms of puffers that people with chronic obstructive pulmonary disease, which often goes along with silicosis, can benefit from. - Participant #3*

Supplemental oxygen may be required as lung function declines.

> *In the end stages or the advanced stages of silicosis, then just oxygen therapy is often used and useful. But none of those things … would slow the progression of the disease, except possibly some of the newer medications that are being looked at. - Participant #3*

> *So, we talk about disease-modifying drugs, but we also need to treat their symptoms of lethargy, fatigue, anxiety, depression, cough. So, need to treat the symptomology as well. - Participant #6*

Access to a specialised occupational respiratory clinic ensures the patient receives integrated care from a multidisciplinary team of specialists.

> *One of the really good things has been setting up the occupational respiratory Clinic at the Alfred and so … we run that clinic two sessions a week. We've got good admin support staff, they're based at the Alfred Hospital. We're linked into a wide range of other respiratory and supportive services. … Having a centralised centre for treatment I think is really helpful. I think it's helped in terms of having a more consistent approach I think in terms of how we actually manage these patients. … It's understanding the cohort, this cohort of young, middle-aged men that have this disease and it's a group of people that have had very little interactions with the medical profession previously. Often they don't have a GP. Their health literacy level is very low. Often just their English language literacy is also very low too. - Participant #7*

> *In particular with our Silica Associate Disease Registry that we've been running for about three years or so now. That's been a really hugely important program through WorkSafe Victoria as well, the screening program to get a really good understanding of this population. So, we've got about 700 people that have been registered in that program, so we've got a good idea of the smoking prevalence, for example. But even things like country of birth, how many come from overseas and need interpreters, all those sorts of things. - Participant #7*

Weight gain is one of the common consequences for workers who have been diagnosed with silicosis and ceased the physically active work in the artificial stone industry. Therefore, maximising fitness through regular exercise is important for keeping fit and avoiding excess weight gain.

> *The biggest issue that I've encountered, considering that lung function has now been quite stable across the cohort, even in severe cases, the biggest issue that we've seen is weight gain. So about two-thirds of the patients have gained weight, and the average weight gain is around six kilograms. The maximum weight gain has been 35 kilograms in the three years of surveillance. So weight gain is a fairly good barometer for a young male who becomes unemployed as to whether they're thriving in the community or not. Most of them drink excessively, that's sort of a maladaptive coping strategy, and gain weight as a result, particularly given that they're not working physically any more. So that's been a big problem for us. - Participant #5*

> *When these workers become patients and they're off work, they've come from very physical jobs quite often, to then be sitting at home not doing anything, they're gaining weight, they lose their fitness and they are increasingly short of breath. How much of that's disease progression versus actually loss of fitness and weight gain is a difficult one for us to tease out. So, getting them into a good exercise program early, so whether it's gym or personal trainer or exercise physiologist or physio or whatever it might be or pulmonary rehabilitation. That's a really important part of it too. - Participant #7*

Pulmonary rehabilitation has been well-researched for patients with a variety of respiratory conditions. For example, a recent meta-analysis of 16 studies reported that pulmonary rehabilitation for patients with interstitial lung disease of any origin was safe and improved functional exercise capacity, dyspnoea and quality of life in the short term and benefits were sustained over a longer term (Table 6).[19] Pulmonary rehabilitation programs included endurance training (e.g. walking, cycling) and strength training exercises and entailed 2-3 sessions per week for eight to 12 weeks. At

follow-up, participants had increased their 6-minute walking distance by approximately 40 metres compared with controls. They also reported less shortness of breath and better quality of life. At 6-12 months follow-up, participants were still able to walk further than controls (mean 37 metres in 6 minutes).

However, the mean age of participants in these studies ranged from 36 to 72 years, which is older than most of the workers in the artificial stone industry. Given that many of the young men with silica-related conditions are in general good health, conventional pulmonary rehabilitation may not demonstrate significant health benefits; and may not be appealing to them.

> *I really can't see that offering much benefit. Most of these young men are actually pretty fit. They're not debilitated. They're not frail, let's put it that way and certainly in my field, pulmonary rehabilitation is most effective in people who have a degree of frailty. ... They can often build muscle mass and improve exercise capacity whereas these guys, their muscle mass is fine which is where pulmonary rehabilitation really provides benefit. It's just that they can't breathe. So, I'm not sure that pulmonary rehabilitation is going to be of much benefit and I think it's highly unlikely any of them would engage because if they're going to be going along to a group of 70-year-old patients with COPD, I think they'd just walk straight out again. - Participant #1*

Whole lung lavage

Whole lung lavage, which involves using a large volume of saline to flush out the materials that obstruct lung alveoli, has been widely accepted for treating pulmonary alveolar proteinosis.[3] In silica-related diseases, the evidence is still limited, but it is considered a safe and effective option for patients with early stage disease. See previous report for details on research published prior to 2020.[1]

More recently, a case series of six artificial stone workers with diagnosed silicosis were treated with whole lung lavage, with promising results.[20] A key aspect of effective outcomes was in the careful selection of patients who were most likely to benefit. The criteria for eligibility included:

- Removed from occupational exposure to silica for ≥12 months
- Worsening symptoms and/or worsening lung function
- Predominant ground-glass opacification (computed tomography scan shows alveoli impacted with large particulate-laden alveolar macrophages)
- Absence of extensive fibrosis.

Whole lung lavage is an invasive process that can only be done in a hospital setting by skilled professionals. The stonemasons in the case series underwent the following procedure. While one lung was artificially ventilated, the other was infused slowly with 8-10ml/kg of 0.9 per cent saline until the outflow was clear. One week later, the same procedure was undertaken for the other lung. All six patients received bilateral lavage in an intensive care setting (1-2 days). Lung function and presence of ground glass opacities was scored before and after treatment using the International Classification of High-Resolution Computed Tomography for Occupational and Environmental Respiratory Diseases (ICOERD) scoring system (0-18). Whole lung lavage significantly reduced the median ICOERD score in five out of six patients (from 7 [interquartile range 6.75-7.25] to 1.75 [interquartile range 1-2.5], p=0.014).[20] The patient showing no change in score had early signs of progressive massive fibrosis. Adverse effects included pulmonary oedema in the lavaged lung (N=4), chest wall soreness (N=3) and vocal cord irritation in one patient.

Whole lung lavage is not suitable for those with established fibrosis, so selecting those who are most likely to benefit is essential.

> *We're quite selective about who may be suitable for whole lung lavage. We believe that that will be most effective in workers … who really have non-fibrotic silicosis. - Participant #1*

> *They need to be highly selected, those patients that have lung lavage. You don't want to do it too early, you don't want to do it too late, and they have to have some evidence of progression. - Participant #7*

> *We're mindful that the evidence base for delivering this treatment is still low. I'm certain there will be a group who will benefit from this and we've seen that in some of our workers and I think it's just a matter of understanding which groups are most likely to benefit and therefore, allocating that treatment. I think the way it'll play out, people with acute silicosis, a lot of crystal, a lot of protein in their alveolar spaces are very likely to benefit from lung washout whereas those that have not much of that, not much crystal burden but a lot of fibrosis, definitely not likely to benefit. - Participant #1*

> *It's a big undertaking and I think we try to really stress that to these patients, this is not coming in for a minor procedure. You're in intensive care essentially for three days and this is everything, patients that have maybe have never set foot in a hospital. So, it can be really very confronting for them. - Participant #7*

To date, evidence of the effectiveness of whole lung lavage for silicosis is limited and there are conflicting views on the benefits, particularly in light of the cost and invasiveness of the treatment.

> *The trouble is, the whole lung lavage is about $80,000 to perform and there may not be any benefit. Hopefully, with the preliminary works … if he can demonstrate an improvement … and also within a year or so document that the disease has stabilised or hasn't progressed, then that may be something that they could do. In selected people it could help to stop progression. - Participant #4*

> *I don't think anything that we're doing now is really making a big difference. Having a whole lung lavage is the way to go. But obviously the challenge is to identify patients who will benefit the most or will progress. - Participant #6*

Given the small sample sizes and lack of a control group, there may be some potential confounders in the data from the stonemasons undergoing whole lung lavage. For example, it is possible that some improvements may have been related to individual behaviours between diagnosis (e.g. silica exposure ceased, quit smoking) and having whole lung lavage treatment.

> *At least one or two of the guys, there was already an improvement in lung function, and possibly in symptoms between the time that I last saw them and had a difficult discussion about their decline and their need for a procedure and when the patient was then seen … and had undertaken the procedure. So in other words, it's quite possible that some of these guys continue to smoke or use drugs and really, the referral and the fear associated with having to go and have that procedure, perhaps changes their behaviour and clears up some of their ground glass nodules and alveolitis even before the procedure does. - Participant #5*

> *So I think that is a real confounding factor in all of this. Because when you look at the guys that we have not sent for whole lung lavage, which is the majority of the guys, even the patients with more significant disease, these are sort of ILO scores of 2/2 or higher, after that initial 12 months, they've been very stable. We've seen a general plateauing of lung function and symptoms, and there's actually been very few patients that are progressively declining in the subsequent two years of follow up as compared to the first year. - Participant #5*

Anti-fibrotic drugs

The evidence supporting the use of anti-fibrotic drugs for treating interstitial lung diseases derives mainly from studies in patients with IPF. Pirfenidone and nintedanib are the only anti-fibrotic drugs recommended in evidence-based guidelines for treating IPF.[4, 21] They have been approved by regulatory agencies worldwide, including Australia. In several large randomised controlled trials, findings have demonstrated significantly lower rates of decline in FVC for patients with IPF assigned to nintedanib (TOMORROW, INPULSUS) and pirfenidone (CAPACITY, ASCEND) compared with a placebo control group.[21] Both drugs have a different mechanism of action and preliminary findings have shown that combination therapy (nintedanib + pirfenidone) is safe and well-tolerated, but clinical effectiveness is not yet known.

> *The studies in pulmonary fibrosis suggests that it roughly halves the rate of decline so it certainly doesn't stop it completely and nintedanib has - there's quite a few side effects that often are dose limiting or even treatment limiting, mainly diarrhoea. …So, a worker with PMF, if they can tolerate nintedanib, may experience a rate of decline that is half of what they would've expected but of course, we don't know what they would've expected anyway and then the trick will be to try and establish treatment without causing too many side effects because PMF is a reasonably slowly progressive disease compared to some of the other forms of pulmonary fibrosis. - Participant #1*

Although there are several other progressive fibrotic lung diseases with similar or overlapping pathogenesis, they are not as well-studied as IPF; however, the evidence of the effectiveness of antifibrotic medications for other non-IPF, progressive interstitial lung diseases, such as silicosis is growing.

The INBUILD trial assessed the safety and effectiveness of nintendanib compared with placebo in patients with various fibrotic lung diseases that are not classified as IPF.[21] Irrespective of the underlying cause, the eligibility criteria included having a progressive interstitial lung disease, decline

in FVC, worsening respiratory symptoms and evidence of lung fibrosis.[22] Results favoured nintedanib compared with placebo (Table 6).

One Participant noted that the Australian Pharmaceutical Benefits Advisory Committee has recently approved nintedanib for patients with progressive fibrosing interstitial lung disease, including silicosis and progressive massive fibrosis. However, nintedanib has yet to be added to the Pharmaceutical Benefits Schedule (PBS); and at present, it is unclear what the specific determination for PBS funding will be.

Pirfenidone has also demonstrated similar improvements. For example, a recent multicentre randomised controlled trial investigated the used of pirfenidone in patients with interstitial lung disease, characterised by progressive lung fibrosis (Table 6).[23] Patients were randomly assigned to receive 2403mg pirfenidone (N=127) or placebo (N=126) daily for 24 weeks. Analyses of home spirometry test scores showed a lower rate of decline in FVC in the pirfenidone group compared with controls; and a slower decline in the mean change for a 6-minute walk test. However, there was no significant difference between groups in the shortness of breath or coughing scales. The most common treatment-related adverse events were gastrointestinal disorders (47% vs 26% placebo), fatigue (13% vs 10% placebo) and rash (10% vs 7% placebo).

However several pirfenidone studies had methodological flaws and findings need to be confirmed in more robust trials.[24] Pirfenidone has not been approved by the PBAC in Australia for treating progressive interstitial lung diseases such as silicosis.

The Australian NiPPS study[25] aims to assess the safety and effectiveness of nintedanib (150mg 2x daily over 3 years) in 100 patients with asbestosis, silicosis, pneumoconiosis and diffuse dust fibrosis. One participant reported that the COVID pandemic has disrupted recruitment for the study. This is not a placebo-controlled trial and patients can be quite variable in their characteristics and responses. Interestingly, several patients who were considered eligible for the trial in 2020 appeared to show some functional improvement that meant they did not fit the inclusion criteria in 2022. These anecdotal observations support a 'wait and see' approach to ensure the right treatment is given to the right patient at the right time.

> *One of the inclusion criteria for that study [NiPPS] was a 10 percent decline in vital capacity over the last one to two years. Just having gone back to the cohort at the 12-month follow up, we had estimated at that time that we would probably have about 25 or 30 patients that were going to be eligible for that trial. With COVID and just funding, getting lung function equipment and training staff to be able to operate that with the appropriate credentials, that's all taken two-and-a-half years. Now it looks like, when we review our cohort, if we apply the same inclusion criteria, we're probably going to have less than five patients that meet the inclusion criteria now. It's an interesting finding. Because if you'd sent a lot more patients for a much more aggressive intervention, like whole lung lavage, three years ago, or two years ago, you would have seen, potentially, that stabilisation of lung function and symptoms, and I think it would have given you a real false impression that it was the intervention that achieved that.*
>
> *- Participant #5*

Robust clinical trials to assess the safety and effectiveness of treatments are difficult to achieve as the prevalence of silicosis is relatively low; and conventional drug development is not appealing to pharmaceutical companies if the size of the potential market is small.[26] Therefore, alternative study designs or approaches may need to be considered, such as off-label use of drugs for diseases with similar pathogenesis or symptomology; molecular techniques to identify targets in the disease pathway; or precision medicine, tailored to an individual's molecular profile.

Lung transplant

Lung transplant is the only option for patients with advanced fibrosis. This was discussed in detail in previous report and there are no notable changes since then.[1]

> *That's not something you want to undertake unless that is absolutely your last resort because median survival is about six years. It's not a cure. ... Even if they were easily available, it is not a long-term option for someone who's 26. You'd want to find other treatment. - Participant #1*

Table 6. Study characteristics and key outcomes of studies investigating treatments for interstitial lung diseases including silicosis

Reference Country	Study design	Intervention Population	Outcomes	Adverse effects
Dowman et al. (2021)[19] Australia	Systematic review/ meta-analysis 5 databases searched (to April 2020) 21 studies	Pulmonary rehabilitation: various programs including walking, cycling, strength training Control: no pulmonary rehabilitation Patients with interstitial lung disease of any origin FU: 3-48 weeks	Physical function • 6MWD: mean difference 40.1 m [95% CI, 32.7, 47.4] vs control Respiratory function • Dyspnoea: SMD -0.36 [95% CI -0.58, -0.14] Quality of life (SGRQ) • Mean change in score: -9.3 [95% CI -11.1, -7.5] Longer term FU (6-12 months): 5 studies • 6MWD: mean difference 32.4 m [95% CI 15.6, 49.3] • Dyspnoea: mean difference -0.29 [95% CI -0.49, -0.10]	• None reported
Wells et al. (2020)[22] UK	Multicentre, double-blind RCT	Nintedanib: 150mg 2x daily 663 patients with a fibrosing interstitial lung disease, not IPF Control: placebo FU: 52 weeks	At 52 weeks: Lung function (FVC): significantly lower rate of decline in nintedanib group vs placebo MD 107.0 [95% CI 65.4, 148.5], p <0.001	Diarrhoea, nausea, vomiting, weight decrease and livre enzyme increases were more frequently reported in nintedanib group vs placebo
Maher et al. (2020)[23] UK	Multicentre, double-blind RCT	Pirfenidone: 2403mg/day Control: placebo 253 adults with interstitial lung	At 24 weeks: Lung function (spirometry) • FVC mean change from baseline: -17.8mL (95% CI -62.6, 27) in pirfenidone vs -113mL (95% CI -152.5, -73.6) in placebo group, p =0.002	Common treatment-related adverse effects: • Gastrointestinal upsets: 47% pirfenidone vs 26% placebo • Fatigue: 13% vs 10% • Rash: 10% vs 7%

Reference Country	Study design	Intervention Population	Outcomes	Adverse effects
		disease, including progressive fibrosis FU: 24 weeks	Physical function (6-min walk test) • 6MWT mean change from baseline: -2.0 m (±68.1) for pirfenidone vs -26.7 m (±79.3) in placebo group, *p*=0.04 Changes in cough symptoms from baseline: NS between groups	

Notes: 6MWD = 6-minute walk distance; CI = confidence intervals; FVC = forced vital capacity; FU = follow-up; RCT = randomised controlled trial; SGRQ = St Georges respiratory questionnaire; SMD = standardised mean difference

NEW AND EMERGING TREATMENT OPTIONS

A growing number of drugs designed to slow or halt the inflammatory and fibrotic processes that are the key features of silica-related diseases are under investigation (Table 7).[4] At the time of publication, none are available in Australia for treating current cases of silica-related disease.

To date, experimental studies have shown that these drugs are potential targets for therapy; and very small clinical studies (<5 patients) on anti-cytokine and antioxidant therapy have demonstrated promising results. However, most are yet to be tested in clinical trials of patients with silica-related diseases.

Table 7. Treatment approaches tested in animal models of silicosis or fibrosis

Treatment	Drug/target
Anti-cytokine therapy	• Anakinra (IL-1ra) • Anti-IL-17 antibody • Anti-IL-9 antibody • IL-13 immunotoxin • Recombinant soluble TNF receptor • Infliximab • Anti-CD-11 antibody
Agents influencing autophagy-lysosomal system	• Imipramine • Dioscin • Rapamycin/cAMP • Atractylenolide III • Trehalose
Antioxidants	• N-acetylcysteine • Corticosteroids • Dexamethasone • Flunisolide
Endogenous glucocorticoids	• Annexin A1
Agents increasing cAMP	• Roflumilast • Tadalafil • Sildenafil
Agents influencing TGFβ	• Emodin • Ponatinib
Other agents	• Rupatadine • Piroxicam • Nicorandil • Hesperetin

Source: modified from Adamcakova [4]

Anti-cytokine therapy

Anakinra is a cytokine receptor antagonist (IL-1), which may be beneficial for improving respiratory function in patients with early stage silicosis.[4, 5] For example, 100mg/day Anakinra given subcutaneously over six months improved respiratory function, oxygen saturation and inflammatory markers in a 37-year-old male with silicosis.[4]

This approach needs to be confirmed and tested in other patients in clinical trials or at least in a series of N-of-1 trials.

Antioxidants - tetrandrine and N-acetylcysteine

Tetrandrine is a calcium channel blocker with anti-inflammatory and immunological effects and N-acetylcysteine is an antioxidant that is used to treat cough and lung conditions. Evidence of their effectiveness for treating silica-related diseases is very limited. Two trials assessed the safety and effectiveness of tetrandrine combined with N-acetylcysteine in patients with chronic silicosis.[15] For example, one trial of 196 patients with silicosis were randomised to usual care (anti-inflammatory, cough and asthma relief) or tetrandrine (60-100mg 3x daily for 6 days per week) combined with N-acetylcysteine (1 tablet, 1-2 x daily). After three months, treatment effects were assessed by lung function tests (FVC and FEV1) and x-rays of lung damage. Compared with the control group, patients receiving the combined treatment demonstrated small but significant improvements in lung function and inflammatory markers.[27] While these results are promising, the findings need to be confirmed in further clinical trials.

Stem cell therapy

Stem cell therapy involves treatment with either mesenchymal stem cells, which can differentiate into various cell types (neuron, bone, cartilage, muscle); or hematopoietic stem cells, which can differentiate into various types of blood cells (red, white, platelets).

Mesenchymal stem cell therapy, which was discussed in the previous review,[1] has been investigated for IPF and shown that is safe to use. Recent studies also suggest that mesenchymal stem cell therapy may improve lung function in chronic inflammatory lung diseases, including silicosis.[28, 29] However, evidence is still very limited.

Complementary and alternative therapies

Several plant-based compounds have been developed to suppress the triggers that activate inflammation or fibrosis.[30] To date, the following compounds have shown promising results in experimental models (rat, mouse), but the safety and therapeutic potential of these compounds have yet to be tested in appropriate clinical trials:

- Sodium tanshinone IIA sulfonate
- Kaempferol
- Astragaloside IV
- Dioscin
- Oleanolic acid
- Hesperietin
- Emodin.

Future potential drug targets

An analysis of the differential gene transcription of the lung tissues of patients with silicosis were compared with those of patients with other lung conditions (e.g. IPF, chronic obstructive pulmonary disease).[31] Data showed that there were common factors across the disorders as well as identifying specific critical genes (MUC5AC, FGF10) that may provide potential targets for silicosis treatment. Plerixafor and retinoic acid were identified as potential candidates for treating silicosis. No trials were identified.

In Australia, the Medical Research Future Fund (MRFF) has funded a program of research into silica-related diseases. One example is the SHIELD study, which involves the use of drug libraries and quantification of lung silica or crystal load in lung lavage fluid material to identify potential biomarkers and targets for treatment. It is only at experimental *in vitro* stage and many years before it comes to clinical trials, unless an existing drug can be identified for off-label use.

> *So, this is all in bench research at the moment, in vitro work but we're using the lung lavage fluid that we've taken from workers who have undergone whole lung lavage. The cells that are in that lavage fluid are the cells that cause the fibrosis so then we're using that material in our in vitro drug discovery platform to identify compounds that have therapeutic potential. - Participant #1*

> *Identified biomarkers that will help with diagnosis and predict future outcome which will be very helpful when trying to make decisions … clinical ones, but also about work and future health etc. - Participant #1*

In another Australian study, Dr Jane Bourke at Monash University has developed an experimental model to investigate the anti-fibrotic effects of Relaxin, a pregnancy hormone. The aim is to determine whether Relaxin, on its own or as adjunctive therapy with existing treatment, can reduce or reverse symptoms of lung disease, including silicosis. Research is currently in pre-clinical phase.

Tailored treatment options

Given the substantial variability in symptoms and complications across patients, tailored treatment and selecting patients with a high likelihood of responding to a particular treatment is likely to achieve optimal outcomes.

> *I would not intervene with nintedanib with every single patient who has even a little bit of lung fibrosis because some of them are going to be quite stable. Equally, you wouldn't want to leave it too long because some of them can progress pretty rapidly so there's going to be a bit of finetuning there to know exactly what to do. - Participant #1*

> *There are more to learn about individual risk factors and why does disease behave differently in different individuals. - Participant #6*

> *They really need individualised care and it's reflecting on things like their smoking history, the duration of in the industry, when they left the industry, what their initial radiology or initial lung function looks like. It really has to be individualised. So, what we've developed is a protocol for when they come through our clinic in terms of the items that we assess when they come through. So, that's been a really good way to actually do it. - Participant #7*

OTHER SILICA-RELATED DISEASES AND COMPLICATIONS

Increasingly, silica dust exposure is being linked with a range of other diseases and complications, including pulmonary conditions (pulmonary fibrosis, sarcoidosis) and autoimmune disorders (rheumatoid arthritis, systemic lupus erythematosus, scleroderma).[2]

Other less well-defined connective tissue disorders have also been observed in silica-exposed workers.

> *I've seen more workers than I think would be normal with other connective tissue disorders, so I'm suspicious that there are other manifestations that are real and happen in these workers that are perhaps not given as much attention as they should be in the literature which largely focuses on scleroderma. - Participant #1*

In Australia, sources of silica exposure remain predominantly in those working with artificial stone installation. While a small number of workers from tunnelling, coal mining and other industries are also at risk, no obvious spike in incidence has been observed as was seen with the artificial stone workers. - Participant #1

Identification of autoimmune disorders in silica-exposed workers can be achieved through various biomarkers and patients can then be referred to rheumatologists.

> *We've got a lot of patients which have blood markers which really indicate they're at a very high risk of developing an auto-immune disease in the future, even if they haven't got symptoms at the moment. But those that have any symptoms of concern we've got a good link with a group of rheumatologists … at St Vincent's. Their area of expertise is in, well a range of things, but also scleroderma and silica-related auto-immune diseases. So, we can refer directly to their service. - Participant #7*

Systemic sclerosis (scleroderma)

Systemic sclerosis, or scleroderma, is a connective tissue disorder with a complex pathophysiology that is characterised by dysregulation of the immune system, inflammation and vascular hyper-reactivity that contribute to uncontrolled development of scar tissue (fibrosis) in the skin and internal organs.[32] Over time, fibrosis causes damage to organs and hardening of the skin, thereby limiting mobility.

Both genetic and environmental factors may play a role in the development of scleroderma, which has three forms:[33-36]

1. Limited or localised scleroderma: affects the skin and subcutaneous tissue and is characterised by patches of thickened skin due to dermal fibrosis. Typically slow and mild course of disease with good prognosis; other organs become involved at late-stage disease[36].
2. Systemic or diffuse scleroderma: affects multiple organs, including skin, gastrointestinal tract, lungs, kidneys, skeletal muscle and pericardium. Other organ involvement occurs early in the disease course; poor prognosis.
3. Scleroderma without sclerosis: a rare form with vascular and fibrotic damage to internal organs, but no skin involvement.[36]

The diverse clinical manifestations of scleroderma present a therapeutic challenge for healthcare providers. Recent research has suggested that patients with scleroderma present with different

clinical features that have four distinct molecular signatures; and may require a more tailored or stratified disease management approach.[32, 37] That is, identifying the treatment that matches a specific molecular signature may lead to a better response in patients with scleroderma.

Several reports have described an association between occupational exposure to silica and development of scleroderma (Erasmus syndrome).[35, 38, 39] While the clinical features are the same, irrespective of the cause, the demographic characteristics of the patients who present with Erasmus syndrome are different. In the general population, scleroderma is more common in women than men, but patients who develop scleroderma associated with silica exposure are more often male.[35] Over 30 per cent of men in an Australian Scleroderma cohort study reported exposure to respirable crystalline silica. Risk of scleroderma was estimated to increase 15-fold in those exposed to silica.[26]

Raynaud's phenomenon

Raynaud's phenomenon is a common early feature of scleroderma, whereby patients experience numbness in the extremities (fingers, toes, ears, nose) and a heightened response to cold. It is characterised by vasospasms of arteries in the extremities, causing decreased blood flow to the extremities. Exposure to cold triggers vasospasms and patients may develop digital ulcers. It commonly occurs in people diagnosed with scleroderma or lupus.

In patients with primary (or idiopathic) Raynaud's, conservative management is recommended, including keeping extremities warm, smoking cessation and avoiding beta-blockers – patients should switch to alternative medications as beta-blockers may worsen symptoms.[33]

However, in patients with secondary Raynaud's, which is associated with scleroderma and lupus, the condition is usually more severe and more likely to lead to complications, such as tissue loss, ulcers and amputations.[40]

Vasodilator therapy, such as nifedipine or amlodipine, may relax small blood vessels and reduce the number and severity of attacks (e.g. vasospasms). Vasodilator pumps have been effective for those who cannot tolerate vasodilator medications.[40] For digital ulcers, prostacyclin analogs and endothelin receptor antagonists have demonstrated benefit. In contrast, botulinum toxin injections have shown limited efficacy in very small studies.

A Cochrane review is currently underway to evaluate the safety and effectiveness of various pharmacological treatments of Raynaud's phenomenon.[40] Results are not yet available.

Scleroderma associated with silica exposure is also more likely to be the limited form (with or without Raynaud's phenomenon), and treatment may require a less aggressive, more conservative approach as the degree of severity is generally milder and less likely to involve other organ systems.[35]

> *There's a higher incidence of the limited. If you look at males who are not exposed to silica, there's a fairly low incidence of scleroderma compared to females. Whereas, in the males that are exposed to the silica, then there's a higher incidence of scleroderma compared to people that aren't exposed.*
> *- Participant #4*

> *Anecdotally, the main differences are that scleroderma is an isolated phenomenon that more commonly affects women whereas this disorder is almost exclusively men because of their exposure. So, I think that's a red flag. For me, if I see a man who has scleroderma, I'll be really, very carefully asking about their occupational history. - Participant #1*

And the evidence for scleroderma is inconsistent. I think if you asked most occupational physicians whether exposure to silica and silicosis increased the risk of scleroderma, most people would say yes, it does. But in the systematic reviews that have been published, the authors of those have generally said the evidence is suggestive, but not definite. - Participant #3

Evidence also shows that silica-associated scleroderma is associated with higher cumulative exposure to silica; and greater morbidity and mortality.[36, 39] Currently there is no curative agent or effective therapies that slow or stop the progression of the condition. However, with early diagnosis and appropriate management of symptoms related to the affected systems, patients may achieve improvement in outcomes.[33] Data from the Australian cohort of workers exposed to silica suggest that the screening program for artificial stone workers may identify the condition at an earlier stage when the symptoms are milder.

Searches identified a very small number of case studies that described the condition, rather than the treatment. No studies were identified that specifically investigated the safety and effectiveness of treatments for silica-related scleroderma.

However, there is a large evidence base on treatment of scleroderma related to any cause. In recognition of the similarity in symptoms, the main findings from the scleroderma treatment research that are relevant to patients with silica-related disease are presented here.

Patient education

Patient education about the disorder is essential. In particular, keeping warm, avoiding extreme cold or trauma to extremities, smoking cessation and exposure to second-hand smoke and monitoring blood pressure to help early detection of renal dysfunction.[33]

Current treatments

Existing treatment options focus on different manifestations of the condition, including pulmonary arterial hypertension, Raynaud's phenomenon, digital ulcerations and renal crisis.[41] Table 8 lists a range of pharmaceutical agents currently used in clinical care for treating scleroderma.[18]

There are four main pharmacological treatments with evidence to support them: cyclophosphamide, mycophenolate mofetil, nintedanib and tocilizumab.[42] Cyclophosphamide and mycophenolate mofetil are the most common agents used for scleroderma; and evidence showed equivalent benefits. Nintedanib and tocilizumab both showed a lower rate of decline in lung function, but no significant effect on skin fibrosis (Table 11).

A systematic review of 14 studies of scleroderma-associated interstitial lung disease reported that use of cyclophosphamide and mycophenolate mofetil demonstrated lower rates of decline in skin fibrosis and lung function (Table 11).[17] Studies that compared the safety and effectiveness of cyclophosphamide and mycophenolate mofetil reported equivalent effectiveness for treating scleroderma, but mycophenolate mofetil was better tolerated as more adverse events were associated with cyclophosphamide (e.g. cytopenia, leukopenia). Not surprisingly, these immunosuppressive agents increased the risk of infections compared with placebo. In contrast, evidence from a meta-analysis of three randomised controlled trials and six open-label studies showed that 12 months of treatment with cyclophosphamide did not improve pulmonary function.[43]

Limited evidence also showed that other medications, including rituximab, pirfenidone and nintedanib were promising alternatives if both cyclophosphamide and mycophenolate mofetil were not well tolerated. However, the findings need to be confirmed in further studies that undertake the same comparisons and assess similar outcomes.

Calcium channel blockers (e.g. nifedipine), endothelin receptor antagonists (e.g. bosentan) and vasodilators (e.g. sildenafil, tadalafil, iloprost) have all been approved for treatment of scleroderma.[41]

However, clear evidence-based recommendations for first-line treatment are lacking; and it is not known what impact these treatments have on the disease progression, or whether the response is sustained.[44]

Table 8. Current treatments for scleroderma

Current standard of care	Evidence
Methotrexate	First-line treatment for early/mild disease; modest efficacy, based on limited evidence from small studies and expert opinion Adverse effects include cytopenia and infections No significant effect on long-term survival
Mycophenolate mofetil	Second-line treatment
Cyclophosphamide	Third-line treatment for more severe disease Adverse effects more common
Nintedanib	Phase 3 trials showed lower rate of decline in FVC, but no improvement in skin tightening Adverse effects were mainly gastrointestinal upsets
Hematopoietic stem cell transplantation	Fourth-line treatment for patients with rapidly progressing disease Adverse effects: higher risk of mortality early in treatment compared with cyclophosphamide; but overall long-term survival is better

Source: Chung and Chung (2020)[18].

Well, a lot of it depends on the manifestation of it, but a lot of it, say for example if they've got bad Raynaud's or CREST syndrome, which is Raynaud's plus calcification, digital ulceration and telangiectasias in their hands and fingers, then you've got to try to treat the - to get a peripheral vasodilator and one of the things is Sildenafil, of all things, or Viagra, at a low dose to cause that dilatation or Nifedipine that helps cause the dilatation. And then, in the bad cases, you can use mycophenolate or methotrexate or prednisone to try and suppress the active inflammation. - Participant #4

Lung conditions

Pulmonary dysfunction in patients with scleroderma requires an interprofessional management team, including a rheumatologist, cardiologist and respiratory physician.[33] A summary of management strategies for lung conditions associated with scleroderma are listed below, but no further data were available.

- **Interstitial lung disease**: Early diagnosis is essential
  - Cyclophosphamide demonstrated benefit for up to 18 months, but was not sustained at 24 months; small studies showed benefits were maintained with azathioprine
  - Mycophenolate mofetil showed improvement
  - Nintedanib slowed the decline of pulmonary function in scleroderma patients with interstitial lung disease
  - Stem cell transplants and anti-fibrotic agents are under investigation
- **Pulmonary arterial hypertension**: Patient education, healthy lifestyle and exercise are essential
  - Supplemental oxygen, diuretics and anticoagulation therapy may be of benefit, as needed
  - Calcium channel blockers are not effective
  - Vasodilator therapy is recommended; prostacyclin therapy is reported to be most effective; or combination therapy for those with severe illness or who fail to respond to one approach.

Gastrointestinal conditions

Conservative treatments for less severe symptoms include exercises to manage decreased ability to open the mouth, good dental hygiene to prevent decay associated with changes in salivary function, sugar-free lozenges or medications for dry mouth, heartburn and reflux.[33] For more severe effects, such as difficulty swallowing (erosive esophagitis) or slow gastric emptying (gastroparesis), proton pump inhibitors and motility agents may be beneficial.

Renal crisis

The only reliable treatment of scleroderma renal crisis is angiotensin-converting enzyme (ACE) inhibitors.[33] Early treatment, at the maximum tolerated dose, is recommended. Despite initial decline in renal function, continued use of ACE inhibitors leads to improvements over time. Prophylactic use of ACE inhibitors is not recommended as it is not effective for preventing scleroderma renal crisis.

Other complications

If left untreated, scleroderma may lead to serious complications, including end-organ damage caused by fibrosis, gangrene due to digital ischemia, malnutrition, pulmonary fibrosis and permanent renal damage.[33]

Treatments under investigation

A recent review also investigated a range of pharmacological agents that were currently under investigation in clinical trials (Table 9).[18] Preliminary data are provided where available; and other trials are still in early stages of recruitment or data collection.

Table 9. Pharmaceutical agents under investigation for treating scleroderma

Agents under investigation	Preliminary data
Biologics	Abatacept phase 2 ASSET trial (N=88): In patients with early scleroderma, abatacept showed no significant difference in mRSS compared with placebo, except in a subset of patients who were identified as normal-type or inflammatory gene expression, the rate of decline in mRSS was significantly better than placebo[45]
Other biologics	Belimumab (Phase 2) Brentuximab vedotin (Phase 1 and 2) Intravenous immunoglobulin (Phase 2) Rilonacept (Phase 1 and 2)
Janus kinase or JAK inhibitors	Tofacitinib or Ruxolitnib, which have been used successfully for rheumatoid arthritis, are promising candidates for treatment as they may potentially impact on both inflammatory and fibrotic pathways.[32] Data from preclinical studies suggest that use of JAK inhibitor medications may slow progression of scleroderma associated with interstitial lung diseases if treated early.[46] JAK inhibition is thought to counteract the effects of lung inflammation and fibrosis, thereby preventing development of serious respiratory symptoms
Tyrosine kinase inhibitors (imatinib, nilotinib, dasatinib) (Phase 3)	Tyrosine kinase antagonists (Imatinib, nintedanib) mediate the fibrotic pathway involved in scleroderma. Early results from a phase 3 clinical trial have shown slowed decline in FVC in patients with scleroderma and interstitial lung disease.[32] A randomised controlled trial was undertaken to assess the safety and efficacy of nintedanib in 576 patients with scleroderma.[47] Patients received 150mg nintedanib, or placebo, twice daily. After 12 months, analyses showed that the rate of decline in FVC was lower in the nintedanib group (-52.4ml per year) compared with the placebo group (-93.3ml per year), p = 0.04 However, there was no difference in the rate of skin fibrosis between the groups Diarrhoea was the most common adverse effect (75.7% nintedanib vs 31.6% placebo).
Vasodilators	Ambrisentan (open label) Riociguat (Phase 2)
Proteasome inhibitor	Bortezomib (Phase 2)

Agents under investigation	Preliminary data
Anti-cytokine therapy (*Anti- IL-13/4; Anti-TGF-β; Anti-IL-1α; Anti-IL-T7; Anti-IL-6)*	Tocilizumab, which inhibits IL-6, did not slow the rate of skin fibrosis.[48] Transforming Growth Factor (TGF-β) is a cytokine that modulates the proliferation of macrophages, thereby regulating the inflammatory process.[32] Early trials involving selective inhibition of TGF-β have shown good safety and tolerance profiles. Romilkimab, which targets both IL-4 and IL-13 that are involved in immunomodulation and fibrosis, showed promising results in skin fibrosis in a phase 2 trial.[32]
Autotaxin inhibitor	GLPG1690 (Phase 2)
B-Catenin inhibitor	C-82 (Phase 1 and 2)
Endocannabinoid receptor agonist	Lenabasum (Phase 3)
Lysophosphatidic acid receptor antagonist	SAR100842 (Phase 2)
Monoclonal antibody to block oncostatin M	GSK2330811 (Phase 2)
ROCK-2 inhibitor	KD025 (Phase 2)

Source: modified from Chung and Chung (2020)[18]

Ongoing clinical trials

The Scleroderma-Lung-Study is an ongoing phase 3 trial that uses a combination of pirfenidone (antifibrotic) plus mycophenolate mofetil (immunosuppressant) to target multiple pathways involved in scleroderma.[32] The study is expected to be completed in September 2022 and results are not yet available.

The SENSCIS study compared nintedanib to placebo in patients with scleroderma and interstitial lung disease.[21]. This study is ongoing, but preliminary analyses showed that nintedanib significantly reduced the rate of decline in FVC compared with those on placebo.[49] There was no significant difference between groups in the skin fibrosis score (mRSS score). Adverse effects were predominantly gastrointestinal upsets (diarrhoea, vomiting, nausea), which were more frequently reported in the nintedanib group compared with placebo. It is not clear whether the combination of mycophenolate and nintedanib provides additional benefit.[50]

Stem cell transplant has been examined as a treatment option for scleroderma and interstitial lung disease. A meta-analysis of three randomised controlled trials reported improvement in quality of life, mRSS scores and lung function (FVC).[37] However, questions still remain about which patients would benefit most from this treatment (comorbidities, disease severity) as well as the optimal protocol to achieve positive outcomes.

While preliminary evidence suggests that stem cell therapy in the early stage of disease may improve skin fibrosis, lung function, quality of life and overall survival rates, there is a higher risk of treatment-related mortality in the period soon after transplantation. The potential benefits need to weighed up against the seriousness of the risks.[44]

Three trials (ASSIST, ASTIS, SCOT) compared autologous hematopoietic stem cell transplant to cyclophosphamide in patients with advanced scleroderma.[44] Each used different techniques, which makes it difficult to compare across trials.

- **ASSIST phase 2** (N=19): Patients were randomised to autologous hematopoietic stem cell transplant with cyclophosphamide or monthly cyclophosphamide for six months. At 12 months follow-up, there was no evidence of disease progression in the patients receiving stem cells, whereas 8/9 patients in the cyclophosphamide arm showed disease progression (measured by FVC and mRSS). Quality of life also increased (measured by SF-36) in the stem cell group and declined in the cyclophosphamide group. Clinical benefits were sustained for up to two years.
- **ASTIS phase 5** (N=156): patients randomised to stem cell therapy (autologous) were at lower risk of death or development of major organ failure compared with those on cyclophosphamide.[44] Pulmonary disease and skin fibrosis improved, but renal function declined and mortality rate was higher during the first year (16.5% vs 10.4% in control arm). Despite this, treatment favoured stem cell therapy over time (2-4 years).
- **SCOT trial phase 2** (N=75): patients were randomised to block treatments of autologous hematopoietic stem cell therapy or cyclophosphamide for 12 weeks.[44] A global rank composite score was used to assess outcomes, including death, failure of event-free survival, FVC, disability, and mRSS. At 54 months follow-up, patients receiving stem cell therapy showed significant improvement compared with cyclophosphamide controls (67% vs 33%). In addition, fewer patients receiving stem cell therapy required additional treatment (9% vs 44%). Treatment-related mortality was higher in the transplant group (6% vs 0% at 72 months), but overall survival was higher in the transplant group (86% vs 51% at 72 months).

Overall, a review of the trials suggested that patient selection was critical (i.e. age, smoking status, existing pulmonary or renal disease).[44] Other questions that need to be addressed include disease severity and comorbidities in patients that failed to meet eligibility criteria for clinical trials.

Many studies are currently underway to determine optimal stem cell therapy regimens, but it is not currently available for interstitial lung diseases in Australia.

It's not going to be a treatment for silicosis because it's not fundamentally an inflammatory disorder. - Participant #1

They sell it [stem cell therapy] across all interstitial lung diseases. I mean, yeah, that gets sometimes, "Can I have a stem cell therapy?" Well, first of all, we don't do stem cell therapy for interstitial lung disease, period, at this point in time. There's really no data to say that it works. Perhaps if they had an autoimmune – I know stem cell therapy is used for progressive systemic sclerosis. That's a recognised indication where they've got a co-existing autoimmune disease and progressive silicosis maybe, but I don't know that anybody's doing the stem cell therapy in Australia for that. - Participant #6

The scleroderma that I've seen … in silicosis has not been aggressive enough to warrant really intensive anti-inflammatory treatment like that [stem cell therapy] so a more standard approach using mycophenolate or other disease modifying treatments is probably more appropriate for almost all of these workers. So, I think it'd be a very, very small, selected group who might benefit from autologous stem cell transplant. - Participant #1

There is no evidence that corticosteroids lead to improvements in function and high doses or long-term use of low-dose corticosteroids have been associated with renal crisis in patients with scleroderma.[15, 33, 51] Only the lowest possible dose for the shortest possible time may be considered if necessary (e.g. for inflammatory myositis, refractory inflammatory arthritis).

Overall, there is a paucity of clinical trials to guide treatment of patients with silica-related diseases. While treatment decisions have been based on lower levels of evidence (e.g. case series, expert opinion) or off-label use of drugs approved for similar conditions, the outcomes are unknown. In the absence of evidence, clinical decisions should be considered with caution. For example, in the PANTHER-IPF study, mortality was higher in patients who were randomised to prednisone, azathioprine and N-acetylcysteine compared with the placebo group.[21] Similarly, anti-inflammatory medications, such as corticosteroids, are not effective if there is no inflammatory activity; and may be harmful in some cases.

Many other clinical trials for scleroderma are currently underway (Table 10).[37]

Table 10. Clinical trials for systemic sclerosis currently underway

Target	Agent	Clinical trials	Phase	Progress
Fibrosis				
IL-1	Bermekimab	NCT04045743	2	Recruiting
Oncostatin M	GSK233308	NCT03041025	2	Recruiting
BAFF	Belimumab + Rituximab	NCT03844061	2	Recruiting
TGF-β	AVID200	NCT03831438	2	Recruiting
PPAR agonist	IVA337	NCT02503644	2	Completed
LPA receptor 1 antagonists	SAR100842	NCT01651143	2	Completed
VEGF	PDRN	NCT03388255	4	Active
Inflammation				
ROCK-2 inhibitor	KD025	NCT03919799	2	Recruiting
JAK-STAT signalling	Tofacitinib	NCT03274076	2	Active
CD30	Brentuximab Vedotin	NCT03222492 NCT03198689	2	Recruiting
T cell activation	Abatacept	NCT02161406	2	Published
Selective cannabinoid receptor type 2 agonist	Lenabasum (JBT-101)	NCT02465437 NCT03398837	3	Completed
Pulmonary arterial hypertension				
TGF-β	Dimethyl fumarate	NCT02981082	1	Recruiting
Thromboxane receptor antagonist	Ifetroban	NCT02682511	2	Recruiting
B cell activation	Rituximab	NCT01086540	2	Active

Target	Agent	Clinical trials	Phase	Progress
Systemic sclerosis – Interstitial lung disease				
GPR84	GLPG1690	NCT03976648	2	Recruiting
Autotaxin inhibitor		NCT03798366	2	Recruiting
Antifibrotic	Pirfenidone	NCT03856853	2	Recruiting
	Pirfenidone + MMF	NCT03221257		
TGF-β signalling	Bortezomib	NCT02370693	2	Recruiting
Bi-specific IgG4 antibody	SAR156597	NCT02921971	2	Completed
B cell activation	Rituximab	NCT01862926	3	Recruiting
Tyrosine kinase inhibitor	Nintedanib	NCT03313180	3	Recruiting
Skin				
IL-17a receptor antagonist	Brodalumab (KHL4827)	NCT03957681	2	Recruiting
Gastrointestinal				
	Rifaximin	NCT04118699	2	Active

IL = interleukin; BAFF = B cell activating factor; TGF-β = transforming growth factor beta; PPAR = peroxisome proliferator-activated receptor; LPA = lysophosphatidic acid; VEGF = vascular endothelial growth factor; IgG4 = immunoglobulin G4; PDRN = poly-deoxyribonucleotide; ROCK = Rho-associated kinases; JAK-STAT = Janus kinas/signal transducers and activators of transcription; GPR = G protein-coupled receptor.

Although there are many different research groups undertaking trials, there are substantial difficulties with recruitment.

> *These young men who all said, "Yeah, yeah, yeah, I'll do it." And then now we go, "Are you coming back?" "No, it's too far. It's COVID." Blah, blah, blah, blah. So, the attrition rates rapidly, we're not getting as many returns as you would like them to be. I think because they've lost momentum. That initial urge, the urgency's no longer there. So, we're not getting end data in as much as we did at the peak of the wave. - Participant #6*

> *We can only do the work with samples and without the samples, it's like, well, you know. We need blood, we need the lavage, we need the tissue. But patients are just reluctant to come forward. Especially with the ones that are stable … At some point some of them will get diseases, important to actually get those groups that have been exposed with no disease and actually find out what's the risk of getting the disease, are there particular markers that actually predict getting disease in the first place?. … But the vast majority will have not progressed, they've left the industry. So, for them it's like, oh yeah, I've left the industry, I haven't progressed, what's the point? - Participant #6*

A case report of a 28-year-old stonemason.[52]

- Diagnosed with Raynaud's phenomenon, scleroderma, interstitial lung disease and pulmonary hypertension – 7 years' workplace exposure to silica.
- Treated with oral glucocorticoids (1mg/kg/day) and methotrexate
  - Reported significant improvement in muscle power and skin tightening, but no improvement in respiratory function.

Table 11. Study characteristics and key outcomes of studies investigating treatments for scleroderma

Reference Country	Study design	Intervention Population	Outcomes	Adverse effects
Flórez-Suárez et al. (2020)[17] Colombia	Systematic review 3 databases 14 studies (2 meta-analyses, 8 clinical trials, 3 retrospective cohort studies, 1 nested case-control study	Various medications: cyclophosphamide, mycophenolate mofetil, nintedanib, pirfenidone, rituximab	Nintedanib • RCT of 576 patients: significantly less decline in FVC vs placebo at 12 months FU (41.0ml/year [95% CI 2.5, 79] • NS difference in mRSS score • NS difference in quality of life score Cyclophosphamide • RCT of 145 patients: significantly less decline in FVC vs placebo at 12 months FU (MD 2.5% [95% CI 0.75, 5.2%], *p*<0.03 • Clinically significant improvement in Mahler Dyspnoea Index score (+1.4±0.23) vs decline in placebo (-1.5±0.43), *p*<0.001 • Significantly less increase in skin fibrosis in mRSS vs placebo (-3.1 [95% CI -3.5, -0.5], *p*=0.008 Combination cyclophosphamide + corticosteroids + azathioprine • RCT of 45 patients: NS differences in FVC, DLCO or dyspnoea score vs placebo Rituximab vs cyclophosphamide • RCT study of 64 patients (open label): significant improvement in FVC% predicted at 6 months vs cyclophosphamide MD 9.5 [95% CI 3.0, 15.9], *p*=0.003 • Significant improvement in mRSS scores: ↓44.4% mRSS with Ritixumab vs ↓23.3% mRSS with cyclophosphamide, *p*<0.001 • Significant improvement in 6MWT: ↑50m with Ritixumab vs ↑13.2m with cyclophosphamide, *p*<0.001	Cyclophosphamide: • NS different in serious adverse effects vs placebo group • Significantly more cases of leukopenia and neutropenia vs placebo

Reference Country	Study design	Intervention Population	Outcomes	Adverse effects
			Mycophenolate mofetil vs cyclophosphamide • Improvements reported in both groups, with NS differences between groups	
Vonk et al. (2020)[42] Netherlands	Systematic review 1 database 77 studies (clinical trials and observational studies)	Pharmacological agents to treat patients with scleroderma and interstitial lung disease	Nintedanib (phase 3 trials) • Same trial as reported in Flórez-Suárez et al. (2020) Tocilizumab (phase 2 and 3 trials) • NS difference in mRSS • Small significant ↓ in FVC decline vs placebo between-group difference 3.4% [95% CI 0.4, 5.6], *p*=0.002 • 9% patients on tocilizumab had ≥ 10% decline FVC vs 25% in placebo group • Quantitative lung fibrosis and lung dysfunction were significantly better in tocilizumab vs placebo group, *p*=0.008 Mycophenolate and cyclophosphamide • Similar outcomes as reported in Flórez-Suárez et al. (2020)	Not reported
Highland et al. (2021)[49] Multinational	Double-blind RCT	Oral nintedanib (150g 2x daily Control: placebo 576 patients with scleroderma and interstitial lung disease FU: 52 weeks	At 52 weeks FU, patients taking mycophenolate at baseline: • Mean annual rate of decline in FVC: -40.2mL/year (SE 19.3) with nintedanib vs -66.5 mL/year (SE 19.3) in placebo; mean difference = 26.3 mL/year [95% CI -27.9, 80.6] At 52 weeks FU, patients not taking mycophenolate at baseline • Mean annual rate of decline in FVC: -63.9mL/year (SE 19.3) with nintedanib vs -119.3 mL/year (SE 19.0) in placebo; mean difference = 55.4 mL/year [95% CI 2.3, 108.5] NS difference in rate of decline between those taking mycophenolate and those not taking mycophenolate	Common adverse effects: Nintedanib vs placebo groups • Diarrhoea: 76% vs 34% • Nausea: 31% vs 16% • Vomiting: 23% vs 12% • Mortality: 10 patients in nintedanib vs 9 in placebo; 1 death in nintedanib associated with study drug •

Reference Country	Study design	Intervention Population	Outcomes	Adverse effects
			Overall, nintedanib reduced the progression of interstitial lung disease in patients with scleroderma, irrespective of their mycophenolate use	
Khanna et al. (2020)[48] US	Multicentre double-blind RCT	Tocilizumab: 162mg weekly infusions Control: placebo 210 patients with diffuse cutaneious scleroderma FU: 48 weeks	At 48 weeks FU • NS difference in mRSS vs placebo	Common adverse events: Tocilizumab vs placebo • Infections: 52% vs 50% • Serious infections equivalent across groups: 13% vs 17% • Cardiac events equivalent across groups: 2 vs 7 events

Notes: 6MWD = 6-minute walk distance; CI = confidence intervals; DLCO = Carbon monoxide diffusion test; FVC = forced vital capacity; FU = follow-up; MD = mean difference; mRSS = modified Rodnan Skin Score; NS = not significant; RCT = randomised controlled trial; SE = standard error; SGRQ = St Georges respiratory questionnaire; SMD = standardised mean difference;

Systemic lupus erythematosus (SLE)

SLE is an autoimmune disorder with variable characteristics that affect multiple organ systems, including skin, heart, lungs, kidneys and gastrointestinal involvement.[44, 53]

Evidence has shown an association between silica exposure and development of SLE, particularly in cases of high exposure to respirable crystalline silica.[54] However, there are few available studies and heterogeneity across studies is high. It is not clear whether the clinical characteristics differ between cases of known silica exposure and other cases of SLE with no known silica exposure. As with scleroderma, SLE is generally more common in women. Risk of SLE was identified in four retrospective cohort studies of workers diagnosed with silicosis, but more evidence is needed to confirm the association.[54]

SLE is commonly treated with immunosuppressants, including corticosteroids, cyclosporine and azathioprine. A monoclonal antibody belimumab (B lymphocyte stimulator) has also been approved for treatment of lupus and has been reported to improve symptoms in approximately 51 per cent of study participants.[44] In contrast, rituximab showed no significant benefit compared with placebo.

Corticotropin injections for persistent active SLE was investigated in a multicentre, double-blind randomised controlled trial (Table 12).[55] There were mixed results, with significant improvement in secondary outcomes (scores for lupus and swollen joints) compared with placebo, but no significant difference between groups in the primary outcome – i.e. proportion of patients with at least 10 per cent reduction in lupus scores.

Bortezomib, a proteasome inhibitor, was investigated in 12 patients with severe lupus and unresponsive to conventional immunosuppressive agents (Table 12).[56] Patients showed significant improvement in lupus measures and markers compared with baseline, and the benefits were sustained for 12 months follow-up. Although this study was limited by small numbers and lack of a control group, it included all patients in Sweden who had received the treatment. Patients were refractory to conventional treatment and had multiple complications, including severe renal involvement, which would normally exclude them from clinical trials.

Stem cell therapy (autologous hematopoietic stem cell transplant) has been investigated in a limited number of studies in patients with SLE, with mixed results ranging from promising to not recommended due to adverse effects. Retrospective studies reported an association between stem cell therapy and a 6-month remission rate of 66 per cent; however, many patients later relapsed.[44] Of the few prospective studies of stem cell therapy in SLE patients, results from the largest study (N=50) suggested that the therapy improved disease markers and overall survival at five years, compared with cyclophosphamide. While adverse events were not common, they were serious – including treatment-related death and severe infections. The mixed outcomes may be related to differences in patient characteristics (comorbidities, disease severity) or differences in the protocols or adjuvant therapies. At this time, larger, well-controlled studies are needed to identify which patients may benefit as well as the optimal regimen for stem cell therapy; and consideration of this approach should be reserved for patients who have few comorbidities (e.g. poor cardiac function) and who fail to respond to current accepted treatment options.

Lymphadenopathy and vasculitis

There is also an association between silica exposure and serum positivity for antineutrophil cytoplasmic antibodies (ANCAs) that affects small and medium-sized blood vessels. ANCA-associated vasculitis is an autoimmune disorder whereby patients experience fatigue and respiratory dysfunction.[57]

> *Everyone had an autoimmune screen, so we have had a few people with a positive ANCA, but then hasn't developed any disease. So, the question we forwarded is are they going to evolve into something in the future? So, we know there was a link with renal disease, we know there was a link with autoimmune disease. I guess only time will tell. … I've seen lots of positive autoimmune tests, but we don't really know what it means in terms of future evolution.*
> *- Participant #6*

Musculoskeletal conditions and rheumatoid arthritis

The risk of developing rheumatoid arthritis was reported to be more than three times higher in people exposed to silica compared with those not exposed.[26]

Very little research on treatments for silica-related musculoskeletal conditions and rheumatoid arthritis was identified.

A recent summary of available treatments suggested that, for the most part, patients respond well to non-steroidal anti-inflammatory agents; whereas antirheumatic medications, such as hydroxychloroquine or methotrexate may be used in more severe, or refractory cases.[33]

Non-inflammatory myopathy was described as more challenging and patients did not respond well to immunosuppressive agents. In those cases, physical therapy and exercise was recommended.[33]

Undefined symmetric polyarthritis, which primarily affects the hands, has been observed in some silica-exposed workers.

> *A lot of them have the aches and pains and sore hands, some of which might relate to their pretty heavy work and some of which might be psychosomatic after the diagnosis being made. They'll often say they didn't have any of this stuff beforehand and as soon as they got the diagnosis, it all started to occur in terms of the aches and pains and joints and muscles. So, it's difficult to sort out sometimes but yes, there's a reasonable amount of rheumatological symptomatology. - Participant #2*

> *We have had patients with non-specific positivity of their autoantibodies, and those patients are probably likely to develop autoimmune disease, they just don't meet the clinical criteria for a connective tissue disease. Those patients tend to have sort of a fairly broad range of positive antibodies. Like they might have a high ANA, high ANCA, or they might have a mild elevated rheumatoid factor. So they just have this broad range of positive autoantibodies, and they've just not developed their autoimmune disease yet. - Participant #5*

A phase II clinical trial (TRAIL1) to assess the safety, tolerability and efficacy of pirfenidone for treating patients with rheumatoid arthritis and interstitial lung disease has been completed; although recruitment did not meet the target sample of 270 due to the COVID pandemic.[58] A total of 123 patients were randomised to daily doses of pirfenidone (2403mg/day) or placebo over

12 months. Participants receiving pirfenidone demonstrated significantly slower decline in lung function, measured by a change in FVC(ml)(-66 vs -146, *p*=0.0082) and FVC% (-1.02 vs -3.21, *p*=0.0028). There was no significant difference in the number of serious adverse events across groups. Although the study lacked statistical power, results showed that pirfenidone is safe for patients with interstitial lung disease and rheumatoid arthritis; and that it slowed the rate of decline in lung function over time. No further data were available.

Tuberculosis and cancers

Cumulative doses of silica increase the relative risk of tuberculosis by 1.5-3.2;[15] and even higher in areas where the background rate is high (e.g. South Africa).[26] Screening for tuberculosis is recommended in silica-exposed workers.[26]

The International Agency for Research on Cancer classified respirable crystalline silica as a Group 1 human carcinogen[59] and evidence of a dose-response relationship has been increasing.[26] Exposure to silica is also associated with higher rates of lung cancer – hazard ratio of 1.3-1.7.[15]

Although few published reports linking silica exposure to development of lung or other cancers were identified, it is possible that they may emerge over time, as the latency between exposure and sings of lung cancer may take decades.

> *Like in WA they've run an asbestos review program for a long time for exposed workers. So, they [workers] can come along and have ongoing periodic monitoring free of charge. There's no doubt that you're going to see significant number of people developing disease later and in particular lung cancer, we're going to see quite a lot that develop lung cancer because of the silica exposure and their smoking history. But that may not be for another 10 years or so.*
> *- Participant #7*

Table 12. Study characteristics and key outcomes of studies investigating treatments for systemic lupus erythematosus (SLE)

Reference Country	Study design	Intervention Population	Outcomes	Adverse effects
Askanase et al. (2020)[55] US	Double-blind RCT	Corticotropin: 80 units subcutaneous corticotropin every 2 days for 4 weeks, then 2x per week to week 16 Placebo Baseline medications: stable glucocorticoids, antimalarials, immunosuppressants 169 patients with active SLE	SLE responder index (SRI-4) = proportion of patients with decreased SLE score • NS difference between groups Number of tender and swollen joints, using 28 Swollen Joint Count/Tender Joint Count (28 SJC/TJC) • Larger reduction in scores from baseline with corticotropin (-6.4±5.7) vs placebo (-4.2±3.8), *p*=0.02 Cutaneous lupus erythematosus disease area and severity index (CLASI-Activity score) • Larger reduction in scores from baseline with corticotropin (-4.5±5.4) vs placebo -2.7±3.1), *p* =0.04	Adverse effects reported more frequently in corticotropin group vs placebo • Upper respiratory tract infection 10.5% vs 1.2% • Insomnia 8.1% vs 4.7% • Headache 7% vs 5.8% • Hypertension 7% vs 0% • Hyperglycaemia 3.5% vs 0%
Walhelm et al. (2021)[56] Sweden	Uncontrolled cohort study of all patients in Sweden treated with Bortezomib	Bortezomib: 1.3mg/m^2 subcutaneously injected in 2-3 cycles on days 1, 4, 8 and 11, with 20-50mg dexamethasone; then 10 days rest before next cycle 12 patients with advanced SLE	SLE disease activity index 2000 (SLEDAI-2k) • Significant reduction in scores from baseline, from mean 14.4 to mean 6.1 at end of treatment period, *p* = 0.003; to mean 4.0 at 6-month follow-up, *p* = 0.007; to mean 4.0 at 12-month follow-up, *p* = 0.008 Physician's Global Assessment (PGA) • Significant reduction in PGA scores at end of treatment period (*p* = 0.03); at 6-month period (*p* = 0.04)	50% (6/12) patients experienced at least one adverse effect Most common were infections: ¼ were serious leading to hospitalisation

Notes: 6MWD = 6-minute walk distance; CI = confidence intervals; FVC = forced vital capacity; FU = follow-up; MD = mean difference; mRSS = modified Rodnan skin score; NS = not significant; RCT = randomised controlled trial; SGRQ = St Georges respiratory questionnaire; SLE = systemic lupus erythematosus; SMD = standardised mean difference

INSIGHTS AND IMPLICATIONS

Options for the effective treatment of silicosis are still limited

While substantial progress has been made over the past 2-3 years in terms of protecting workers in the artificial stone industry through engineering controls, licensing, screening and health surveillance, the options for effective treatment are still limited.

Typical treatment options for silicosis disease management

Removal from workplace

Key support includes smoking cessation, psychological support, routine health surveillance to monitor disease progression, vocational training and support for return-to-work

'Wait and see'

For patients with no or mild symptoms, a conservative approach may be sufficient for managing symptoms as they arise

Whole lung lavage

For eligible patients with evidence of lung opacities, but without established fibrosis

Anti-fibrotic medications

For patients with early signs of fibrosis, nintedanib may be considered

Lung transplant

For patients with more advance disease, such as massive pulmonary fibrosis

Research into an array of different pharmacological agents is currently in progress, but most are still in pre-clinical or early clinical trials and may take years before there is sufficient evidence to establish safety and effectiveness. Other approaches, such as identifying specific biomarkers (e.g. SHIELD study) to characterise the disease characteristics, stage of disease or for partitioning patients into different treatment options are also in early experimental phases. Relevant biomarkers may be useful for identifying potential treatment options amongst existing drugs used safely for other similar indications (i.e. off-label use).

Return to work

While a positive diagnosis is a shock to the cohort of young and generally healthy workers in the artificial stone industry, the need to leave the industry is also a major setback that can be very challenging and psychologically distressing.

The point of view of these patients is "Can we cure the disease and can we get them back to work in something that they enjoy doing that is going to be as financially rewarding as the job that they've just had taken away from them?" That's hard, especially with COVID and especially the way jobs are at the moment. - Participant #2

Return to work is highly important in this group. It's about finding suitable work for them and how you define suitable. So, they really go through … sort of different stages of grieving once they've been given a diagnosis. … Sometimes the workers feel like they've been given a job just to try and get them off the insurance books and "you're not our problem anymore". You can have a job packing boxes at a factory. You're capable of doing that, but it's a lot less money. They're not with their friends. It's an unskilled job. It's how you actually support them through that to actually provide that individualised return to work management without it being seen as being the insurers trying to save a bit of money. - Participant #7

In some cases, there is conflict between the return-to-work strategy and a compensation payout. The payout is determined according to the definition of a 'terminal' illness, which includes anything that might shorten a person's life, even if that is by less than 12 months.

Individual occupational physicians and individual respiratory physicians will give quite varied answers on that [return-to-work]. So we have no real unified approach to returning to work. I think that has been a big barrier to retaining and reemployment. - Participant #5

So if you've got the potential of receiving that $700,000 or $800,000 terminal payout from the government, you're not really keen on engaging in any ongoing work, because that identifies that you're capable of working, and being retrained, and being reemployed and continuing to work. …. Most of those guys have just put their lives on hold for two-and-a-half years whilst they await the outcome of their terminal payout. … If you've got an unwilling population of workers who have a far better option that being retrained, which is to get a huge payout reasonably easily, then that's going to hamper your efforts. … Getting a return to work strategy that was universally agreed upon by occupational physicians and respiratory physicians in Queensland two years ago, would have been incredibly helpful. - Participant #5

I suppose the greatest shock to the system is how many of these people are not able to go back to work or willing to go back to work, and how expensive it is going to be to maintain them into the future on basically WorkSafe benefits? I think that's quite a shock to everyone's line of thinking. - Participant #2

Competing interests

There are also potential competing interests between those providing medical advice and those providing legal advice.

For example, workers may be given legal advice not to disclose smoking or drug-taking behaviour as it could impact on their compensation case; but non-disclosure of substance use may impact on their health management strategy.

Even though I have a good rapport with all of these guys, they're very reluctant to tell you about what goes on at home, just because they perceive - and possibly quite rightly - that it will maybe negatively impact their Medico Legal case. They generally have very strong advice from their lawyers not to disclose any recreational drug use or ongoing smoking. So we don't - at this point in time, haven't done any random drug tests on any of the guys. But they almost, 100 percent of the time, will deny that they've used any recreational drugs. But each individual will tell you how rife it is amongst the cohort generally, and because they know each other. - Participant #5

Once they've been unemployed for a period, their focus is how they can really get as much compensation out of the system as they can as quickly as they can. That's been a big barrier to us. Because it's hard to have a conversation with a person about their physical or mental health when they're just trying to make everything sound as bad as it could possibly sound for the purposes of getting as much money out of the compensation as they can. - Participant #5

It's important to have separation of roles between a treating physician and the compensation process so that decisions are made independently.

So I think they really needed to have a primary respiratory physician, and then anyone providing Medico Legal reports probably needed to be completely independent to my process with them. - Participant #5

What next?

The workers who stay in the industry are 'in the system', irrespective of whether they have a silicosis diagnosis; and they get what they need in terms of support, health care and surveillance. For example, all workers who are negative for silicosis, but stay in the industry, will still be monitored as a requirement of licensing. In contrast, when workers leave the industry, it is unknown what happens later if they develop a silica-related disease.

It's about 200 or so that have got a positive diagnosis in that registry and the rest have been screened and don't have a diagnosis. So, the ones that don't have a diagnosis, they're the ones we worry about because if you've got a diagnosis then typically you have a WorkCover insurance claim, you're in the system, your medical expenses are covered. You'll come back and see me or another respiratory physician periodically. The cost of the CT imaging and lung function, any medical expenses is covered. But there's this group and the ones in the screening registry it's probably about, I don't know, maybe half or maybe a third of the actual population that's out there. We worry because that group has got no screening longitudinally unless they stay in the industry. That's a big problem. - Participant #7

So, essentially you've got probably in Victoria about 2,000 workers that worked in a highly hazardous work environment for 15 to 20 years. So, when you're working with engineered stone, dry processing, it was really, really common. In our registry, there was almost nobody that wasn't exposed to some dry processing. We know that there can be a latent period between that exposure and development of disease. So, even though they weren't picked up when they had attended screening over the last two years, there's still a significant risk of

disease, especially those that are smokers, lung cancer risk as well as silicosis. So, having a dedicated free ongoing health monitoring program or however it's termed, I think it's going to be really vital to that group of people. - Participant #7

Importantly, the screening and health surveillance needs to be appropriately managed to ensure all workers are screened and followed up.

If you just say to people, "You need to do screening," often it's done as a tick and flick exercise. So, there really needs to be good oversight of what that screening actually has been. - Participant #7

Other industries, such as mining and tunnelling, also involve silica exposure and, while the incidence of silica-related diseases may be lower than in the artificial stone industry, workers should be entitled to the same protections.

CONCLUSIONS

A two-pronged approach is needed to manage both the risks and the consequences of exposure to silica in the workplace. This includes a strong regulatory system that protects workers from exposure in the first place. While silica exposure is known in many industries, there is also a need to identify other potential sources of exposure and implement appropriate protections before another generation of workers is affected.

Where exposure is inevitable, screening routinely for early identification of positive cases is essential. If workers are diagnosed early and no further silica exposure occurs, disease progression may slow down. However, the longer-term outcomes are still unclear, even in the absence of further exposure.

Current treatments for occupationally-acquired silica-related diseases remain limited as there are **no proven therapies** to reverse or halt disease progression once it has started. The only option is to manage symptoms and complications as they arise. Beyond the physical symptoms, workers must also deal with the psychological sequelae of a positive diagnosis and the trauma of losing their jobs. Therefore, a high level of support in these areas is essential, particularly in the early days after a diagnosis, but also for the longer period while they seek an alternative rewarding job.

While there are some promising treatments under investigation, none will be available in the near future. As the disease and its associated complications progress, treatment becomes more challenging and the available options decrease.

Therefore, management of claims for the current cohort of workers with occupationally-acquired silica-related conditions requires an individually tailored approach, matching the right therapy to the patient who is most likely to benefit.

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