Spring/Summer 2013

Newsline

HPS Pharmacies

HPS Partners with Genesis CancerCare

to Deliver Oncology Pharmacy Services On-site

Plus:

Expanding Pharmacy Services with Little Company of Mary Health Care, and HPS Pharmacies' Annual Gala Dinner and Awards Night

HPS Pharmacies

Sponsorship

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Cover Image
(Left to right) Michael Davis, General Manager, Genesis CancerCare, with Loan Nguyen, Pharmacy Manager, and Zeyad Ibrahim, National Oncology Manager at HPS Pharmacies.

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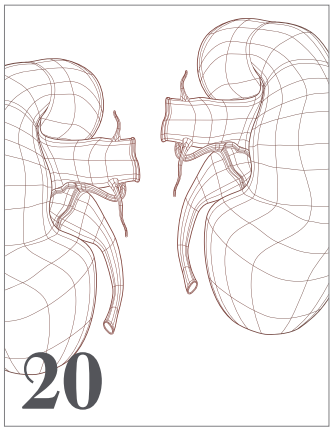

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Message from Tony Wyatt CEO

As we greet the New Year with renewed focus, we can thank 2013 for delivering a year of progressive strategic growth and advancements in our national footprint, resultantly setting new industry standards in pharmacy services and patient care.

Our goal for expansion was met and exceeded as HPS Pharmacies found homes in six new sites across Australia, in particular the unveiling of our first owned and operated pharmacy in the West Australian market. Oncology has been a principal focus for HPS Pharmacies in the last year with a number of our new sites offering critical oncology services.

However a period of deficient funding for the preparation and dispensing of chemotherapy infusions has placed significant pressures on the industry. Following more than 12 months of lobbying from many advocacy groups, including *Professionals for Safe Cancer Treatment* in which I am personally involved, the Coalition Government have provided a positive outcome in the interests of patients, pharmacists and the wider pharmacy community. The commitment to funding affords certainty for oncology in line with the next Guild Agreement.

The announcement is a significant step forward in sustainable care for cancer patients and reinstates oncologists and pharmacists back to the frontline in patient treatment. As Australia's largest pharmacy service provider, we recognise the importance of protecting the future viability of services, within an environment of continuous policy changes, which can have a significant impact upon health.

Our commitment to standardised business practices was reflected in HPS Pharmacies recent CEO Open Forum, in which employees were given the opportunity to candidly discuss their thoughts on practices and services at site level. As Chief Executive Officer, it gave me the occasion to investigate our operational effectiveness at ground level and discuss with our internal community where they feel HPS Pharmacies' energy, time and focus must be invested in the future to align with the needs of our employees. The forum signifies HPS Pharmacies' dedication to solidifying the business' position as employer of choice within the pharmacy industry.

It is inspirational reflecting on the strong performance of the past 12 months, and I anticipate a continuation of this growth and success, as we look to exciting initiatives in the coming months. I look forward to the journey ahead alongside our dedicated staff and valued clients, as we work together to set industry standards and fortify HPS Pharmacies as the nation's leading pharmacy services provider.

Tony Wyatt
Partner / Chief Executive Officer

Message from Steve Yeo COO

2013 has proven a fruitful year for HPS Pharmacies producing phenomenal operational growth, diversifying by six new sites across the Australian market. It is a credit to the efforts of the entire HPS Pharmacies community that our business has solidified its national footprint with representation in every state in Australia, as well as implementing services within the Northern Territory.

In line with HPS Pharmacies' strategic plan for growth, a new position was created to ensure that our expanding operations carries with it the appropriate support to ensure we are achieving the maximum value for our clients, and maintaining a workforce with a strong culture.

The General Manager – Operations is a pivotal leadership role in our Senior Management team, providing ongoing operational support and performance guidance to all HPS Pharmacies sites.

The role is representative of our expanding Operations division and is crucial in achieving standardised operational procedures, fortifying HPS Pharmacies' relationship with our clients through improved performance and delivery of services. I was excited to formally introduce Jeremy Stones to the business as General Manager – Operations during our recent Management Group Conference. To read more, please turn to page 12.

Standardisation and quality of services was a particular focus for this year's exclusive annual Management Group Conference (MGC) held in South Australia. Productive and innovative once again, the 2013 MGC held a strong team focus, serving as a key opportunity for effective communication and collaboration on developing site level initiatives.

Emphasis was paid to cultivating standardised practices and readjusting our focus to align with the strategic performance and future endeavours of HPS Pharmacies.

This distinctive event is vital for the growth of our business as it provides an opportunity for senior management to collaborate, learn and educate, ensuring a united vision and pathway for HPS Pharmacies is fostered.

The augmented format of this year's event delivered several key suppliers an invaluable and enviable platform to present to our business' entire national management group, proving fruitful for all.

I look forward to observing the flow-on effects achieved for our suppliers and clients as a direct result of the initiatives developed during the MGC, as HPS Pharmacies strives to enhance our position as Australia's leading pharmacy service provider.

Steve Yeo
Chief Operating Officer

Feature Article

HPS Pharmacies

This page: Michael Davis, General Manager, Genesis CancerCare, with Loan Nguyen, Pharmacy Manager, and Zeyad Ibrahim, National Oncology Manager at HPS Pharmacies.

Cover page: Michael Davis, General Manager, Genesis CancerCare, with Loan Nguyen, Pharmacy Manager, and Zeyad Ibrahim, National Oncology Manager at HPS Pharmacies.

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HPS Partners With Genesis CancerCare

> *I am of the view the quality of Genesis CancerCare has been greatly enhanced as a result of the support from HPS Pharmacies...*
>
> – Michael Davis, General Manager, Genesis CancerCare, Western Australia

In June 2013 HPS Pharmacies was successful in securing an on-site pharmacy with new client Genesis CancerCare, in one of Australia's fastest growing regions, Joondalup, Western Australia.

Genesis CancerCare is a provider of both radiation and medical oncology services, with a national network of comprehensive cancer centres across Australia through a vision of sustainable care and excellence in specialist services.

Genesis CancerCare is a state-of-the-art development located at Shenton House in Joondalup, featuring ten chairs and three oncologists all serviced by HPS Pharmacies. The on-site pharmacy delivers oncology pharmacy services, including a dispensary, and isolators for cytotoxic drug preparation, under the expertise and guidance of HPS Pharmacies' National Oncology Manager, Zeyad Ibrahim.

Located on Level 2 of Shenton House, the HPS Pharmacies site provides patients with the convenience of a one-stop location for cancer treatment and related needs. On-site manufacturing of chemotherapy provides renewed assurance to nurses and oncologists that urgent supplies can be obtained with ease for their patients. Additionally, it permits the Clinical Pharmacist to deliver a follow up service including clinical intervention, advice and counselling to patients of the Genesis Medical Oncology Ward.

Zeyad Ibrahim says HPS Pharmacies delivers a tailored service to Genesis CancerCare, committed to quality assurance and exemplary patient care.

"Patients will be astounded at the quality of the facilities and the level of support offered by staff. This is a direct result of the collaborative nature of HPS Pharmacies and Genesis CancerCare to provide the best care possible".

General Manager, Genesis CancerCare Western Australia, Michael Davis, says HPS Pharmacies have exhibited numerous strengths in the construction of the new site, including the speed and efficiency in establishing services and the dedication paid to partnership building and long-term vision.

"As we have been constructing Shenton House and its provisions, HPS Pharmacies has been by our side assisting with technical expertise and guidance, both from a clinical and regulatory perspective. I am of the view the quality of Genesis CancerCare has been greatly enhanced as a result of the support from HPS Pharmacies".

Pharmacy Manager, Loan Nguyen, has been instrumental in the project and says the new pharmacy site has offered previously unavailable services and knowledge to medical oncology staff.

"The provision of a Clinical Pharmacist to counsel, clarify information and answer patient questions has been invaluable to patient care and treatment. Through mock training exercises, in consultation with Genesis CancerCare's medical oncology staff, we have fostered strategies for optimal delivery of services that meet the needs of our patients".

Securing the Genesis CancerCare contract at Joondalup has delivered significant value to HPS Pharmacies as it strengthens its national chemotherapy footprint, and marks the unveiling of its first owned and operated pharmacy in the West Australian market.

The implementation of the new site to Joondalup provides a real alternative to cancer patients who previously had to travel 30kms into the city for treatment.

HPS Pharmacies has strived to collaborate and foster a positive relationship with Genesis CancerCare from the beginning and in the eyes of Michael Davis it has exceeded this expectation.

"I would describe the relationship as a partnership. We have worked together as a team from the start to establish a world-class service with enormous potential. It is exciting to be in such a unique position to provide the highest quality of medical oncology care available in Western Australia".

HPS Pharmacies look forward to expanding its services across Western Australia with many exciting projects in the west on the horizon, and further strengthen its presence as the leading national provider for pharmacy services.

This page: Sharon Kendall, Chief Executive Officer at Calvary Central Districts Hospital, with Trudy Pannach, Pharmacist In-Charge at HPS – Calvary Central Districts, and Dominic Coppola, Partner/Regional Operations Manager – SA/WA/NT at HPS Pharmacies.

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Expanding Pharmacy Services with Little Company of Mary Health Care

HPS Pharmacies has enjoyed a long-standing partnership with Little Company of Mary Health Care for a number of years, and it is with great pleasure and elation that we announce the opening of a new on-site pharmacy at the purpose built Calvary Central Districts Cancer Centre in Adelaide. The state-of-the-art facility delivers vital services to cancer patients in Adelaide's North, including a 12-chair cancer day centre, on-site radiology and specialist consulting rooms.

HPS Pharmacies' investment with Calvary Central Districts Cancer Centre has assisted to alleviate pressure for health services in the area, as the surrounding community increase their demands for greater accessibility to resources.

The on-site pharmacy delivers oncology and general hospital services, including a dispensary, oncology clean room, and isolator for cytotoxic drug preparation. Functionality has increased within the cancer centre, as a result of the new HPS Pharmacies facilities providing a wide range of products and services for patient treatment in a timely manner.

The duality of the site as both an oncology manufacturing facility and on-site pharmacy caters for the on-demand requirements of the hospital. Calvary Health Care Adelaide Business Development Manager, Jeniffer Jelicic, praises the new facility for its ability to cater for the varied service requirements of the hospital.

"HPS Pharmacies' staff are committed, focused and approachable, assisting with all areas of concern on request. The pharmacy service delivery on-site at Calvary Central Districts Hospital offers a seamless responsive service for patients, staff, and doctors".

HPS Pharmacies' facility offers clinical aid to patient's bedside and expert pharmaceutical product counselling, all sustained and aided by clinical support to staff through educative tools, drug use evaluations, imprest reviews, and drug information and advice. Newly appointed Calvary Central Districts Hospital Chief Executive Officer, Sharon Kendall, brings a wealth of local knowledge and private hospital experience, and credits HPS Pharmacies in the contribution to quality patient care within the hospital.

"HPS Pharmacies plays a crucial role in patient education, promptly providing key tools such as medication profiles that detail the medical history for patients and establish at-home treatment plans in collaboration with their GP".

Trudy Pannach, Pharmacist In-Charge at HPS – Calvary Central Districts says HPS Pharmacies has provided fundamental benefits to the delivery of oncology treatment, particularly in relation to the increased efficiency and speed in attending to patients.

"It is my hope that collaboration with the radiotherapy suite here at Calvary Central Districts Hospital will provide a one-stop shop for oncology patients".

> *"The pharmacy service delivery on-site at Calvary Central Districts Hospital offers a seamless responsive service for patients, staff, and doctors."*
>
> – Jeniffer Jelicic, Calvary Health Care Adelaide Business Development Manager

HPS Pharmacies' Partner and General Manager – Hospitals, Tin Huynh, shares this vision and says further investment with Calvary was an easy decision to make.

"The decision to invest in the development of the on-site pharmacy with a modern sterile suite and medication dispensing pharmacy was an easy one, as it was a natural extension to the existing services HPS Pharmacies already provided. The on-site facility delivers a responsive and quality dispensing and oncology pharmacy service to the existing hospital and the new cancer centre. The modern sterile suite allows just-in-time tailoring of chemotherapy infusions and provides the patient with an all-encompassing pharmacy service from the time they arrive at the hospital to the time they are discharged".

Solid foundations were laid for a robust partnership between HPS Pharmacies and Calvary Central Districts Hospital over the previous years of collaboration, which continues to grow in strength with HPS Pharmacies' presence on-site. Partner/Regional Operations Manager – SA/WA/NT, Dominic Coppola, says the partnership is one of mutual understanding and respect.

"We work together in partnership to achieve a common goal of outstanding services offered to our clients and their patients. On behalf of HPS Pharmacies I would like to thank Jeniffer for her support and contribution to our partnership during her time as Acting Chief Executive Officer, and welcome Sharon to her new role as Chief Executive Officer at Calvary Central Districts Hospital. We look forward to a future of growth with Calvary Central Districts Hospital and are excited to further strengthen our long-standing partnership with Calvary".

This page: (left to right) Winners of HPS' Annual National Awards – Ian Bell, Ben Tait, Jean Ang, Tina Chan, Choi-Ling Batten and Yianni Sotiriou, with Tony Wyatt and Dr. Andrew Holsman (centre).

HPS Pharmacies' Night at the Circus

November 2013 was an exhilarating time for HPS Pharmacies as the Annual Gala Dinner and Awards Night burst onto the calendar like a circus into town, with over 130 HPS employees and their partners revelling in the unique festivity.

Sanctuary Adelaide Zoo provided a creative and playful venue for a Night Circus themed Gala Dinner with mischievous mime artists, a jolly juggler and curious contortionist ushering attendees through a memorable night of sumptuous food and lively music in commemoration of the business' success throughout 2013.

Delicate tea candles and canapés lent perfectly to an opening mood of celebration as attendees reflected on the significant contributions from HPS Pharmacies' national teams. A fixture on HPS' annual event calendar, the national awards epitomise HPS Pharmacies' core values of excellence, innovation, and leadership, commending the achievements of individual team members and overall teams across a range of categories.

The six awards, introduced and presented by HPS Pharmacies' Chief Executive Officer, Tony Wyatt, and Chairman of the HPS Board, Dr. Andrew Holsman, include:

"The Dr. Holsman Award for Innovation", recognising outstanding innovation at any level of the organisation;

"Corporate Team Member of the Year", recognising that individual whose conduct and contribution had a profound impact upon the business and its employees;

"National Pharmacy Manager of the Year", recognising the outstanding leadership of a Pharmacy Manager within a team environment;

"National Site of the Year", recognising the leading HPS Pharmacies site for financial and team performance;

"National Pharmacist of the Year", recognising the company's most outstanding pharmacy professional for contributions to HPS, its clients, and the field of pharmacy within healthcare; and

"National Pharmacy Technician or Courier of the Year" recognising that individual whose conduct and contribution had a profound impact upon the business and its clients.

The annual national awards, introduced as a new initiative within the business in 2011, encourage the recognition of high performers and promote a culture that nurtures value, diligence and fellowship.

Tony sees the awards as "an opportunity for peers to pay their respects and take ownership in celebrating those individual stars who contribute in HPS Pharmacies' ongoing success."

The winners have been immortalised on HPS' Honour Board at HPS Pharmacies' Corporate Office in Adelaide.

The Annual Gala Dinner and Awards Night was the conclusion to another vigorous and prolific Management Group Conference (MGC). South Australia again played host to the annual MGC, in picturesque Hahndorf in the Adelaide Hills, with an eventful 'Amazing Race' theme leading the way in education, standardisation and innovation.

Attendees participated in team building activities, role-plays and an "Amazing Race" through Main Street, which provided an interactive element to an information-dense three day conference. Strategies were developed to standardise industry practice and improve efficiency in the delivery of services to clients.

Tony said "the highly interactive environment created by HPS Pharmacies' management team, brought unity and standardisation to the foreground and presented a shared vision for the business' endeavours into the New Year. There are encouraging signs for 2014 off the back of a strong performing 2013, and we look forward to announcing more exciting initiatives soon."

National Award Winners

Congratulations to our award winners who have been immortalised on HPS' Honour Board at HPS Pharmacies' Corporate Office:

1. **The Dr. Holsman Award for Innovation**
   Ian Bell
   (HPS – Corporate Office, South Australia)
2. **Corporate Team Member of the Year**
   Yianni Sotiriou
   (HPS – Corporate Office, South Australia)
3. **National Pharmacy Manager of the Year**
   Choi-Ling Batten
   (HPS – Hobart, Tasmania)
4. **National Site of the Year**
   HPS – Brunswick
   (Victoria)
5. **National Pharmacist of the Year**
   Jean Ang
   (HPS – Alexander Avenue, South Australia)
6. **National Pharmacy Technician or Courier of the Year**
   Ben Tait
   (HPS – Ringwood, Victoria)

From The Team

Jeremy Stones

General Manager – Operations

I recently joined HPS Pharmacies as General Manager – Operations. This role has been created in line with HPS Pharmacies expansion and ongoing strategic plan for growth. Using my extensive operations management experience in both domestic and off-shore environments, I can assist to cultivate this growth and further strengthen the Operations division.

I look forward to working with the Regional Operations Managers, Pharmacy Managers and Pharmacist's In-Charge, to ensure our structure, processes and frameworks facilitate this growth.

HPS Pharmacies has made an exceptionally positive first impression, in particular the dedication and conscientiousness of its employees in delivering high quality pharmacy services. This reflects HPS Pharmacies' position as market leader and sets the industry benchmark.

The recent Management Group Conference was an enlightening introduction to the business operations of HPS Pharmacies. It provided a unique opportunity for our Management and Executive Teams to share ideas, network and bring standardisation, the company's direction and shared vision to the forefront. It additionally provided an effective platform to brainstorm concepts to further enhance our competitive advantage.

I am delighted to be leading the Operations team as HPS Pharmacies enters a period of transformational change and executes its clearly defined strategic plan.

Vicki Poupoulas

Pharmacist In-Charge, HPS – Flinders

The *39th SHPA National Conference* was recently held in Cairns to the theme of 'Get Smart, Get Personal and Get Inspired'. Sessions reflected this theme, demonstrating how we can develop as health professionals through further education, improve our practice via technology, and 'Get Smart'.

By assisting each other across disciplines, we enhance our delivery of patient care and tailor evidence-based medicine to meet our individual patients' needs and 'Get Personal'. As the pharmacy industry is operating within rapidly changing and progressively more challenging times, we need to see this as a time of growth and opportunity, and 'Get Inspired'.

The *Quality Care Pharmacy Program (QCPP)* is an area where we can apply the *SHPA* theme, as HPS Pharmacies works through the national reaccreditation process in 2014 to facilitate a unified approach when providing patient care and professional services.

Accreditation provides many benefits for both pharmacies and their patients, ultimately with patients confident their *QCPP* accredited pharmacy is compliant with industry and professional standards, and affiliated staff are trained to provide the highest level of patient care.

In the coming months, I look forward to continuing to deliver our clients with an innovative, inspired and personalised approach, which will fortify HPS Pharmacies' position as leading supplier in pharmacy services.

Nicki Jackson

Procurement and Contracts Manager

The Procurement team have worked diligently over the past twelve months to deliver three rounds of PBS Price Disclosure, with changes in April and August affecting a large number of items. A conscious effort was made by our team to ensure these changes were managed seamlessly to certify minimal disruptions to our sites and clients.

Additionally, the Procurement team have been responsible for ordering all the fixtures, equipment and consumables required for the day-to-day operations of six new HPS Pharmacies sites across Australia. Our team designed new and enhanced merchandising solutions and product mix to meet the needs of the individual sites, working to implement stock management and ordering processes.

In 2012, key suppliers were invited to participate in an inaugural procurement forum where future business was discussed and agreed upon. Due to its success, this event will be repeated in 2014 to further develop the relationships with these valued suppliers, and provide mutually beneficial outcomes.

Additionally, a number of these suppliers were afforded an opportunity to present valuable information on products and future developments at our recent Management Group Conference.

The new format proved fruitful for our suppliers taking advantage of the rare opportunity to present to HPS' entire national management team in a dedicated and uninterrupted forum. We hope to see this augmented forum implemented again next year to further support the continued growth of HPS' remarkable supplier relationships.

Ian Bell

Chief Information Officer

HPS Pharmacies' IT team prides itself on its dynamic and extensive service, helping to provide outstanding front-line support to customers and clients.

Since 2012 our teams' focus has been to maximise productivity and job satisfaction, ensuring IT is delivering innovative and efficient systems and solutions. Internal employee reviews have indicated an increase of over 30% in overall satisfaction, with a total of 97.6% of people pleased with our service delivery.

This positive feedback brings a renewed energy to the team as we look to the future to enhance client knowledge of the opportunities the HPS Pharmacies IT team can deliver, and capture the creative network of ideas to reinforce the business' position as the leader for industry innovation.

A vision for mobile technology is currently under development, adding a new layer of patient care which sees instantaneous patient records available bedside for our pharmacists. ClinPod® will soon undergo a makeover; delivering tablet-based servicing to our clients with a new dimension in technological services.

We are eager to collaborate at site-level to gain a tailored understanding of the areas and opportunities IT can further refine, ensuring a steady stream of improvement and unity with our customers and clients.

Pharmacy Business

Worldwide medicines shortage

Medicine shortages tripled between 2005 and 2010 in some countries, and continues to worsen, with growing concerns for the serious potential of future medicine shortages worldwide.

Shortages occur when:

- There is only a single, or very few, suppliers of a key ingredient;
- When countries don't manufacture domestically;
- Quality standards become ever more stringent; or
- When a country has limited economic capacity (as seen in Greece's economic crisis).

Shortages also arise from increased demand, when newer therapies are more effective, the ageing population needs more, from shortages of related products, or as prescribing guidelines change (such as the penicillin G spike in Australian hospitals, which the sole provider couldn't satisfy).

An array of stakeholders from across the globe recently gathered at the *International Summit on Medicines Shortage* to examine the various causes and to propose solutions. These included national formularies, however improved demand predictability could create monopoly markets with diverse negative consequences. Market forces don't always protect supply; seen when protamine sulphate production in China was ceased as manufacturers reacted to a large price reduction.

The Summit concluded with six major recommendations:

1. Make information about medicine shortages publicly accessible in a timely manner;
2. Identify and list critical/vulnerable products for each country;
3. Develop procurement processes to facilitate continuity of supply;
4. Align transparent regulatory practices within and between countries;
5. Appoint one national body to provide guidance, and to gather and disseminate information globally; and
6. Develop evidence-based risk management strategies for supply continuity.

They observed that "medicines should not be considered as ordinary commodities of trade" and that medicinal social goals can't always be achieved in a free market.

Reference:

1. Besançon L, Chaar B. *Report of the International Summit on Medicines Shortage; 2013 June 20-21; Toronto, Canada*. The Hague: International Pharmaceutical Federation; 2013.

Pharmacists to "Continue Dispensing"

In certain emergency situations, pharmacists in some States may supply a few days' worth of Schedule 4 medicines without a prescription to enable continuity of therapy.

The *5th Community Pharmacy Agreement (5CPA)* has expanded this autonomy to allow pharmacists to also offer patients one continued dispensing service annually where the full quantity of the medicine is supplied, and funded through the *Pharmaceutical Benefits Scheme*. This service is limited to oral contraceptives, and cholesterol lowering HMG CoA reductase inhibitors ('statins').

In order to provide this service, the pharmacist must verify that the patient needs to continue their established and stable medicine immediately, but is unable to visit a medical practitioner. Circumstances where this may happen include when the patient is away from home, about to embark on a holiday, or has simply finished their last repeat of medicine without getting a new prescription. The pharmacist has a duty of care to refer the patient to a medical practitioner if therapy has been intermittent or compliance inconsistent.

The medical practitioner must be identifiable, and have reviewed the patient since the medicine was commenced, the dose changed, or at least within the last year.

While the *5CPA* has been in place for three years, this incentive was only due to start September 1st 2013, however it is still awaiting individual state-based legislation to be passed before it can actually commence.

Reference:

1. Pharmaceutical Society of Australia. *Guidelines for Continued Dispensing of Eligible Prescribed Medicines by Pharmacists*. Canberra: PSA; 2012.

Schedule negotiations may be too public

On Saturday 1st February 2014 alprazolam will become a Schedule 8 poison. On this day, all stocks must be transferred into a drug safe, and documented as for other controlled drugs.

Alprazolam was selected from an original proposal to reschedule all benzodiazepines partly because the 2mg tablets are now by far the most common of all forged prescriptions since flunitrazepam set the lead in 1997. While there was an overall decline of 8% in demand for benzodiazepines under the *Pharmaceutical Benefits Scheme (PBS)* between 2002 and 2009, alprazolam demonstrated a contradictory increase of 28%.

Compared with other benzodiazepines, alprazolam does not show any improved clinical benefit. However, it is more often abused because the potent action and rapid elimination trigger more severe withdrawal symptoms. It may also be more toxic when overdosed.

Mr Stephen Marty, Chair, *Pharmacy Board of Australia*, has expressed concern over the public nature of discussions around the assignment of alprazolam to Schedule 8. Mr Marty fears this will provide the public a chance to stockpile it for later use (or misuse), and potentially increase the risk of hold-ups, burglaries and forgeries.

Sales by one major wholesaler have so far remained relatively flat over the first nine months of 2013, whereas *PBS* dispensing reports show a decline of more than 20% during the same period, possibly reflecting the administrative barrier of prior authority approval.

Healthcare facilities are often proactive in protecting their staff from drugs with a potential for abuse, by applying discretion to increase controls without waiting for government mandate. This may be a time to step ahead of the pack.

References:

1. Delegates of the Secretary to the Department of Health and Ageing. *Reasons for scheduling delegate's interim decision and invitation for further comment*. Canberra: Medicines and Poisons Scheduling Secretariat. May 2013.
2. Department of Human Services. *Pharmaceutical Benefits Schedule Item Reports, Medicare Australia Statistics*. Canberra, Australia.
3. *Public submissions on scheduling matters referred to ACCS #7, ACMS #8 and the joint ACCS-ACMS #5 (March 2013)*. p. 1–194.

Accreditation in Pharmacies

Like many industries, pharmacies are required to undergo accreditation. The Quality Care Pharmacy Programme (QCPP) was introduced nationally in 1998 by the Pharmacy Guild of Australia, to ensure services provided to the community are compliant with industry standards. In 2011, the QCPP was recognised as Australian Standard 85000:2011 quality management system for pharmacies in Australia.

The original ten key elements which pharmacies were assessed against have evolved over time, moving away from a dispensing focus, towards being an integral member of a healthcare team and delivering on the professional practice initiatives (PPIs) of the Fifth Community Pharmacy Agreement (5CPA).

Pharmacies are now assessed every two years against eighteen elements ranging from legal and employment obligations through to delivering health programs, services and quality improvement. Each element has a list of actions a pharmacy must be able to demonstrate; a current process, as well as documented evidence to meet the standard.

Today over 90% of pharmacies are accredited across Australia, where these standards have become the framework to ensure a uniform approach of the delivery of service to the community, as well as instilling a culture of continuous quality improvement in the industry.

This year, three HPS Pharmacies sites in South Australia were reaccredited for QCPP and achieved outstanding results; Morgan House (HPS – Alexander Avenue and HPS – Corporate Office) in May and both HPS – Ashford and HPS – St Andrew's in August.

Using N-acetylcysteine in the Treatment of Bipolar Disorders

Lisa Rudolph, Pharmacist In-Charge
HPS – Melbourne Clinic, Victoria

Bipolar disorders are relatively common psychiatric conditions with a lifetime prevalence of up to 4%. At least a quarter of sufferers will have a history of suicide attempts, with 10-20% of all patients ending their life by their own hand. Relapse, the recurring nature of the condition unless adequately treated, can gradually take its toll on the patient's quality of life. The average patient experiences a major relapse every 17 to 30 months, with episodes frequently lasting between three and six months.

There are a variety of conventional mood stabiliser medications used in the treatment of bipolar, such as lithium and several antipsychotics and anticonvulsants. These drugs are an important component of treatment but may leave some patients with a shortfall in their recovery. The challenge for many clinicians is to ensure adequate long-term control of bipolar. Thus, new treatments are continually being sought from novel pathways with better efficacy profiles.

Over the years, the pathophysiology of bipolar disorder has continually been refined. The relationship between cell loss in specific regions of the brain and bipolar disorder is well documented. Recently however, the focus of research has been to further investigate how the oxidative pathways of 'free radicals' are linked to bipolar disorder and thus, the new types of treatment options available.

Free radicals are present in normal physiological processes and serve essential biological purposes in cellular signalling, immunological and inflammatory responses. Normally the free radicals are counterbalanced by a scavenging system. However, in disease the free radicals have the potential to cause cellular dysfunction and damage; this is known as oxidative stress. There are two theories on how the body can undergo oxidative stress; the first being dysfunction of the mitochondria in the brain, and the second is dysfunction of the primary antioxidant 'scavenger' glutathione (GSH).

Mitochondria are structures inside cells which generate the body's energy. The mitochondria can become damaged during oxidative stress and impairment of the mitochondria can lead to further oxidative stress and cell death. In turn, GSH is vulnerable to depletion during oxidative stress. These two processes can create a vicious cycle of damage and disrupt cellular homeostasis. Thus, interventions that restore GSH balance can intervene in this cycle of oxidative damage and prevent long-term illness.

GSH is not orally bioavailable. Synthetic versions of oral GSH and L-cysteine (precursor to GSH) have been ineffective due to poor blood-brain barrier transfer and/or first pass metabolism. However an agent that has been gaining increasing interest is N-acetylcysteine (NAC). NAC, also known just as acetylcysteine, is the N-acetyl derivative of the amino acid L-cysteine and is the precursor to the in vivo formation of glutathione. Oral administration of NAC allows good blood-brain barrier penetration and therefore increases in GSH levels. NAC can reverse mitochondrial toxicity; it has robust antioxidant effects and can enhance neurogenesis and reduce inflammation.

The discovery of NAC in the treatment of bipolar has been a case of an old medicine with a new indication. NAC has been used in the treatment of paracetamol poisoning for over 30 years. Newer indications include its use as a mucolytic, treatment of HIV, and in contrast-induced nephropathy. NAC can also be purchased from health food stores as an antioxidant supplement.

The results of some preliminary studies are positive in demonstrating the efficacy of NAC. In a recent 6-month double-blind, randomised, placebo-controlled study by Berk and colleagues, 2000mg daily of NAC or placebo was added to the existing treatment of 75 bipolar disorder sufferers.

Participant symptoms were measured using various rating tools such as the *Montgomery-Asberg Depression Rating Scale (MADRS)*, the *Bipolar Depression Rating Scale*, the *Quality of Life Enjoyment and Satisfaction Questionnaire*, etcetera during the study, and also after completion of the study. Of significance was the difference in scores of the *MADRS* (a strong measure of depression) where the NAC group scored nine points better than placebo at endpoint, although similar at washout.

The recommended dose of NAC for bipolar is two x 500mg capsules, three times a day. Some side effects of NAC may include gastrointestinal upset (such as diarrhoea, constipation, nausea and heartburn). Rare side effects include aggravation of asthma, stomatitis, rhinorrhea, fever, and sedation.

Since its use in bipolar disorder, there has been growing interest in the use of NAC in other fields of psychiatry including addiction, obsessive-compulsive disorder, trichotillomania, grooming disorders, and schizophrenia. These initial results appear positive and require further research. NAC may also provide an opportunity for an alternative treatment option for these areas of psychiatry where current treatment options are limited or suboptimal.

References

1. Angst J, Sallero R. *Historical perspectives and natural history of bipolar disorder.* Biol Psychiatry 2000; 48: 445–57.
2. Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaitz I, et al. *N-acetyl cysteine for depressive symptoms in bipolar disorder – a double blind randomised placebo-controlled trial.* Biol Psychiatry 2008; 64(6): 468–75.
3. Carlson PJ, Drevets WC, Manji HK, Singh JB, Zarate CA. *Neural circuitry and neuroplasticity in mood disorders: insights for novel therapeutic targets*. NeuroRx 2006; 3(1): 22–41.
4. Dodd S, Dean O, Copolov DL, Malhi GS, Berk M. *N-acetylcysteine for antioxidant therapy: pharmacology and clinical utility.* Expert Opin Biol Ther 2008; 8(12): 1955–62.
5. Halliwell B. *Oxidative stress and neurodegeneration: where are we now?* J Neurochem 2006; 97(6): 1634–58.
6. Kessler RC, Berglund P, Demmler O, Jin R, Merikangas KR, Walters EE. *Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication.* Arch Gen Psychiatry 2005; 62: 593–602.
7. Scalley RD, Donner CS. *Acetaminophen poisoning: a case report of the use of acetylcysteine.* Am J Hosp Pharm 1978; 35(8): 964–7.
8. Schieke S M, Finkel T. *Mitochondrial signalling, TOR, and life span.* Biol Chem 2006; 387(10–11): 1357–61.
9. Zarate CA, Singh J, Manji HK. *Cellular plasticity cascades: targets for the development of novel therapeutics for bipolar disorder.* Biol Psychiatry 2006; 59(11): 1006–20.

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Management of Chemotherapy Induced Nausea and Vomiting

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Amongst the many toxicities associated with chemotherapy, nausea and vomiting remain among the most feared adverse effects for cancer patients during their treatment. With the development of a number of effective and well tolerated antiemetics, significant progress has been made in the management of chemotherapy induced nausea and vomiting (CINV).

If not effectively controlled, CINV can significantly impact quality of life for cancer patients, adding to the morbidity and cost of treatment.

Several guidelines have been developed and recently updated, with recommendations for antiemetic use in the prevention of CINV; these include the *American Society of Clinical Oncology (ASCO) Antiemetic Guidelines*, the *National Comprehensive Cancer Network (NCCN) Antiemetic Guidelines* and the *Multinational Association of Supportive Care in Cancer (MASCC) Antiemetic Guidelines*.

Vomiting occurs due to the stimulation of a multistep pathway which is regulated in the brain. This involves stimulation of the vomiting centre (located in the medulla) by the chemoreceptor trigger zone (CTZ), gastrointestinal (GI) tract, vestibular system, psychological mechanisms, and intracranial activity. The neurotransmitters dopamine, serotonin (5HT3), histamine, acetylcholine, corticosteroids and neurokinin-1 mediate this stimulation, and are each found in varied proportions in the GI tract, the vestibular system and the CTZ. Chemotherapy, or its metabolites, can activate these neurotransmitters, leading to emesis.

Nausea and vomiting may also be associated with anxiety, or can be a learned response. As chemotherapy has the potential to cause nausea and vomiting in a number of ways rather than through one specific pathway, there is no single antiemetic agent that can be used to prevent all CINV.

CINV can be classified as either acute, delayed, anticipatory, breakthrough, or refractory. Acute onset emesis occurs within the first 24 hours of chemotherapy, with the intensity usually peaking at five to six hours after drug administration. Delayed nausea and vomiting occurs more than 24 hours after chemotherapy. Anticipatory emesis occurs before a patient receives their treatment, and is a conditioned response which occurs in those who have had significant nausea and vomiting with previous chemotherapy.

Breakthrough emesis is that which occurs even if prophylactic antiemetics have been given. In these cases, rescue antiemetics are required. Refractory emesis refers to emesis that occurs after treatment cycles where patients no longer respond to first-line prophylactic and rescue antiemetics.

Chemotherapeutic agents vary significantly in their ability to cause emesis. Intravenous and oral chemotherapy drugs are classified as either high (occurring in more than 90% of patients), moderate (30-90%), low (10-30%) or minimal (<10%) emetic risk. Other factors which may increase the risk of CINV include: female gender, previous chemotherapy, previous chemotherapy associated emesis, being younger than 50 years of age, and no history of alcohol consumption.

Commonly used antiemetics for CINV include serotonin (5HT3) receptor antagonists, neurokinin-1 receptor antagonists, corticosteroids, dopamine receptor antagonists and benzodiazepines. 5HT3 receptor antagonists include palonosetron, tropisetron, ondansetron, granisetron and dolasetron. These are most effective in the prevention of acute CINV.

Palonosetron is a potent second generation 5HT3 receptor inhibitor, which can be given as a single dose prior to chemotherapy because it has a long half-life (approximately 40 hours). It is now the preferred 5HT3 antagonist. Neurokinin-1 receptor antagonists include aprepitant and fosaprepitant (the IV formulation).

Emetic Risk	Acute (Day One)	Delayed (Days Two – Four)
High Option 1	Aprepitant 125mg PO; or Aprepitant 165mg PO day 1 only;* or Fosaprepitant 115mg IV Dexamethasone 12mg PO/IV 5HT3 antagonist	Aprepitant 80mg PO days 2–3 Dexamethasone 8mg PO days 2–4
High Option 2	Dexamethasone 20mg PO/IV 5HT3 antagonist	Dexamethasone 8mg PO bd days 2–4
Moderate	Dexamethasone 8mg PO/IV Palonosetron 0.25mg IV	Dexamethasone 8mg PO days 2–3
Low	Dexamethasone 4–8mg PO/IV; or Metoclopramide 10–20mg PO/IV; or Prochlorperazine 10mg PO/12.5mg IV	Nil
Minimal	Nil (unless patient has previous history of nausea and vomiting)	Nil

Table 1. Antiemetic Guidelines According to Emetic Risk

** During May 2013, Aprepitant 165mg as a single dose one hour prior to chemotherapy on day one, was made available on the PBS to replace the current three day dosing schedule.*

When combined with 5HT3 receptor antagonists and dexamethasone, aprepitant can provide significant additional antiemetic effects for both acute and delayed nausea and vomiting.

Dexamethasone is the most commonly used corticosteroid in CINV management. It is used synergistically with other agents and can help manage delayed emesis. Dopamine receptor antagonists, including metoclopramide, domperidone, and prochlorperazine, are generally used for breakthrough and refractory emesis, while benzodiazepines are reserved for anticipatory nausea and vomiting. Antihistamines like promethazine and cyclizine are also used in the management of acute, delayed and refractory CINV.

The aim of antiemetic treatment is to prevent nausea and vomiting; with optimal management of the acute phase required to prevent emesis in the delayed phase of treatment. To prevent acute CINV, antiemetics should begin prior to administration of chemotherapy and should cover the first 24 hours of treatment.

Antiemetics chosen should be based on the chemotherapy drug with the highest emetogenic risk in the patients' treatment regime, as well as any patient specific risk factors, and previous experiences. Patients may also modify their eating habits to reduce CINV, such as eating smaller, more frequent meals and avoiding foods that make them feel nauseous. A summary of the antiemetic guidelines for the prevention and management of CINV can be found in Table 1.

Managing breakthrough emesis can be challenging as it is easier to prevent than to treat CINV. Treating breakthrough emesis requires giving an additional antiemetic agent from a different drug class with a different mechanism of action. There may be a need for regular dosing rather than as required, or to change antiemetic therapy to a higher level, such as from moderate emetic risk to high emetic risk.

Anticipatory emesis is ideally controlled by optimal prevention of acute and delayed CINV. Psychological and behavioural techniques should first be used to help prevent further anticipatory nausea and vomiting. In some cases benzodiazepines may be used as an alternative or additional treatment, such as lorazepam 0.5mg to 2mg the night before and the morning of treatment.

Chemotherapy administered over multiple days does not have a specific antiemetic regimen, and recommendations are difficult as acute and delayed CINV can potentially overlap. Recommendations vary depending on the types of protocols used, as the degree of acute and delayed CINV depends on the emetogenicity of the individual drugs and the sequence of administration.

The *MASCC* and *NCCN Guidelines* recommend a 5HT3 antagonist and dexamethasone be given before doses of moderately or highly emetogenic chemotherapy on each day, and with dexamethasone continuing for two to three days after for protocols likely to cause delayed CINV. Aprepitant may also be used in protocols with high emetic risk that have delayed CINV.

References

1. Basch E, Prestrud AA, Hesketh PJ, Kris MG, Feyer PC, Somerfield MR, et al. *Antiemetics: American Society of Clinical Oncology clinical practice guideline update*. J Clin Oncol 2011, 29(31): 4189–98.
2. Cancer Institute NSW. *Prevention of chemotherapy induced nausea and vomiting*. Protocol ID: 7 Version 2. Eveleigh: Evi Q cancer treatments online; 2013.
3. Gralla R, Roila F, Tonato M, Herstedt J. *MASCC/ESMO Antiemetic Guidelines 2011*. Hillerød: Multinational Association of Supportive Care in Cancer; 2011.
4. NCCN Antiemesis Panel. *NCCN Clinical Practice Guidelines in Oncology – Antiemesis*. Version 1. Fort Washington: National Comprehensive Cancer Network (NCCN); 2012.
5. Palliative Care Expert Group. *Therapeutic guidelines: Palliative Care*. Version 2. Melbourne: Therapeutic Guidelines Limited; 2005. p. 209–16.

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N-acetylcysteine and the Prevention of Contrast-Induced Nephropathy

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N-acetylcysteine

N-acetylcysteine (NAC) is an acetylated derivate of the amino acid, cysteine. It can be administered via oral, intravenous (IV) or respiratory routes. NAC is used commonly as a mucolytic agent in various respiratory conditions such as emphysema, bronchitis and cystic fibrosis. Inhalation of NAC leads to splitting of disulphide bonds between the glycopeptides in viscous mucus, and loosening of obstructive plugs.

IV NAC is also an effective antidote for paracetamol overdose. The reactive metabolite of paracetamol, N-acetylbenzoquinoneimine, depletes the liver's antioxidant stores of glutathione and damages hepatic cells directly, causing acute liver failure.

NAC provides cysteine as a substrate for the synthesis of more glutathione and prevents liver damage when given within eight hours. Glutathione and acetylcysteine bind to, and detoxify, the reactive metabolite. Glutathione stores are also replenished, preventing further oxidative cell injury.

Contrast-Induced Nephropathy

Contrast-induced nephropathy (CIN) is a common and serious complication after the administration of iodinated contrast media used in radiological diagnostic and interventional procedures. CIN is generally described as an increase in serum creatinine of at least 0.5mg/dL (44.2 µmol/L), or more than 25% above the baseline value after exposure to a contrast medium. The increase in serum creatinine level usually begins shortly after the completion of the procedure, peaks at three to five days, and returns to baseline within one to three weeks.

The risk factors associated with the development of CIN are the following:

- Pre-existing renal insufficiency,
- Diabetic nephropathy,
- Age > 70 years,
- Volume depletion,
- Anaemia,
- Heart failure,
- Hypotension,
- Concomitant use of nephrotoxic drugs such as NSAIDs, diuretics, aminoglycosides, amphotericin B, ACE inhibitors, angiotensin II receptor antagonists, some immunosuppressants (e.g. cyclosporin), and various chemotherapy agents (e.g. cisplatin),
- High dose of a contrast medium (>125mL), or a repeat dose within 72 hours, and
- Type of contrast medium; high-osmolar contrast media are more nephrotoxic than low- or iso-osmolar agents in patients with pre-existing renal impairment.

Creatinine clearance calculated using both the Cockcroft-Gault and the Modification of Diet in Renal Disease (MDRD) formulae are better for estimating the glomerular filtration rate (GFR), than using only serum creatinine levels.

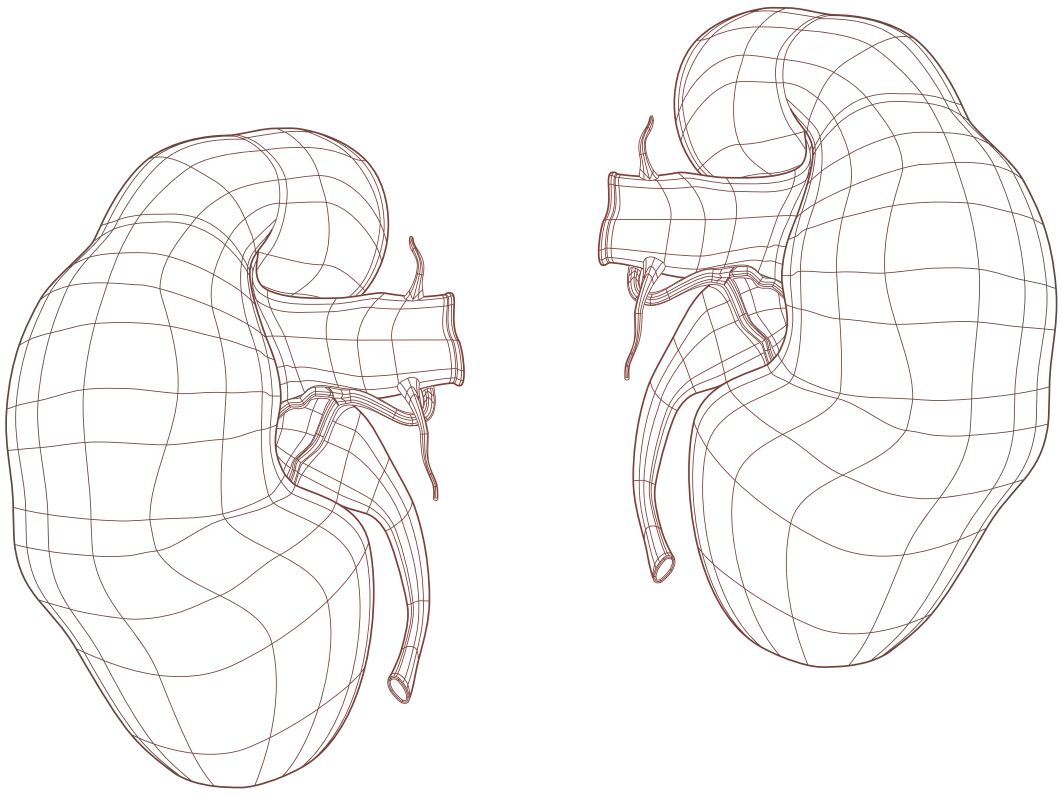
The MDRD formula is currently used by pathology laboratories in Australia and New Zealand, and an estimated GFR (eGFR) figure is routinely provided whenever a serum creatinine level is reported. It is suggested that patients with an eGFR of <30mL/min are at highest risk.

Prevention of CIN

The nephroprotective mechanism of NAC is postulated to be due firstly to its antioxidant properties, thereby decreasing oxidative tissue damage generated by the contrast media, and secondly its vasodilatory effect, leading to an improvement in renal blood flow and a reduced risk of developing CIN.

NAC was first shown to be effective in reducing the incidence of CIN in patients with chronic renal dysfunction by Tepel in 2000. Since then, multiple trials have been conducted but the results were conflicting and inconsistent. Meta-analyses have found a high level of heterogeneity across these studies therefore definitive conclusions could not be made.

In 2011, the *Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT)* was published. It found that NAC does not reduce



the risk of CIN in at-risk patients undergoing coronary and peripheral vascular angiography.

It is important to note that although the *ACT* is a large multicentre randomised controlled trial, like many trials there were limitations. The patients were at lower risk (the procedures were being done for diagnostic rather than interventional purposes) and a lower volume of contrast dye was used (100mL) etc.

As there is some evidence of its efficacy in preventing CIN, NAC is still used in clinical practice. It is inexpensive, safe and is well tolerated by patients. Except in emergency situations, oral administration is preferred because most of the available evidence has been demonstrated with this route, and because IV NAC is associated with a minor risk of anaphylactoid reactions.

It is suggested that the original Tepel dosage should be used i.e. 600mg twice daily on the day before and the day of contrast exposure.

In clinical trials, 600mg or 1200mg has been well tolerated. Gastrointestinal discomfort and dizziness have been reported. Patients should also be warned about the "rotten-egg" smell of NAC.

This can be minimised by proper dilution. When using the commercial 20% vial of NAC, each dose of 600mg/3mL or 1200mg/6mL can be diluted in at least 10mL or 20mL, respectively, of a cola drink or other soft drink (or water only if NAC is given via nasogastric tube). The preparation is not stable beyond one hour, hence it should be mixed just before use.

The only well-established strategy for the prevention of CIN is the periprocedural administration of IV fluids to avoid volume depletion. Sodium chloride has been studied the most and isotonic saline (0.9%) is preferred over hypotonic (0.45%) solutions.

It has also been postulated that alkalinising renal tubular fluid may be beneficial, as free radical formation is promoted in an acidic environment but inhibited at a higher pH.

As free radicals increase the risk of developing CIN, alkalinisation with isotonic sodium bicarbonate may reduce the risk of renal cell injury. Note that patients with heart failure or on dialysis, however, should not receive fluid loading.

Interestingly, theophylline has been studied for this indication. After exposure to the contrast agent, the renal concentration of adenosine increases, causing vasoconstriction thereby impairing renal blood flow.

Theophylline is an antagonist for adenosine receptors and is thought to prevent the development of CIN by improving renal blood flow. Trial results on theophylline have been conflicting. However, it is said that it offers additive protection to saline hydration and oral NAC.

The usage of theophylline clinically to prevent CIN may be problematic, as it may interact with the patients' medications such as macrolide antibiotics, fluoroquinolones, rifampicin, phenytoin, carbamazepine, barbiturates, and cimetidine.

Note that other drugs such as mannitol, frusemide, simvastatin, iloprost, dopamine, fenoldopam, calcium channel blockers, and ascorbic acid have also been evaluated. They have not been found beneficial in preventing CIN and are therefore not recommended.

If possible, nephrotoxic drugs should be discontinued up to 48 hours before the procedure. Metformin should also be withheld to avoid the risk of lactic acidosis, should acute renal failure occur. Avoid using high osmolar contrast media in patients with renal impairment. Renal function should be monitored 48 hours after contrast administration.

Conclusion

The impairment of renal function following exposure to a contrast medium is usually transient, however may be permanent in some cases. The treatment for established CIN is limited to supportive measures and dialysis.

Therefore, screening for high-risk patients and having appropriate preventive strategies are important. The benefits of performing contrast media-enhanced procedures in these patients need to be weighed against the risks of developing CIN.

The decision to perform these procedures however, should not be influenced by the availability of NAC due to its inconsistent efficacy in preventing CIN.

References for this article can be found in the online version published in the HPS Pharmacies Knowledge Centre.

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Bevacizumab (Avastin)

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Bevacizumab is a recombinant humanised monoclonal antibody that has been trialled for a variety of indications including colorectal, breast, ovarian, renal cell cancers, non-squamous non-small cell lung cancer and glioma. Bevacizumab inhibits angiogenesis which in turn inhibits tumour growth and the spread of cancer.

Angiogenesis, the complex formation of new blood vessels, is a normal physiological process that is essential in tissue growth, foetal development, and wound healing. Existing blood vessels are also remodelled and expanded. Angiogenesis is essential for the growth of tumours over 1-2mm in diameter. It also aids the spread of cancer to other parts of the body (metastasis).

Angiogenesis facilitates the delivery of essential components and is triggered by multiple stimuli including oxygen and glucose deprivation in cells. Anti-angiogenic factors are also released during normal physiological regulating processes. This balance is disrupted in cancer cells, which favour angiogenesis and the spread of the cancer.

Diseased or injured cells release multiple growth factors including proangiogenic Vascular Endothelial Growth Factor (VEGF). VEGF binds to receptors on the endothelial cells that line the interior surface of blood vessels and promotes permeability and cell growth, making more nutrients available to tumour cells. The VEGF receptor pathways also promote cell survival, cell migration and the production of tissue factors.

Bevacizumab binds to, and neutralises, the VEGF receptors to inhibit tumour growth and metastasis. VEGF is overexpressed in cancer cells, resulting in bevacizumab's preferential action in tumour cells, making it a targeted therapy.

Multiple drug regimens are often more effective, and thus preferred, over monotherapy for cancer treatment, however the adverse effects may multiply. As the side effect profiles of targeted therapies like bevacizumab differ from traditional chemotherapies, they can be successfully added to many existing regimens without exacerbating adverse effects, making them an ideal choice.

Although different from chemotherapy, bevacizumab still has many potential adverse effects; increased risk of blood clots, bleeding, low blood cell counts, diarrhoea, impaired wound healing, anorexia, weakness, myalgia, dizziness, pain, headache, hypertension, proteinuria, fever and an increased risk of thromboembolic events including stroke, heart attack and angina. Serious side effects include osteonecrosis of the jaw, pulmonary hypertension, nasal septum perforation, gastro-intestinal perforation, hypertensive encephalopathy and reversible posterior leukoencephalopathy syndrome. Patients may experience hypersensitivity reactions including shortness of breath or anaphylaxis.

Infusion related reactions may include high or low blood pressure, flushing and chest pain. If any serious adverse effects occur, the infusion should be stopped immediately.

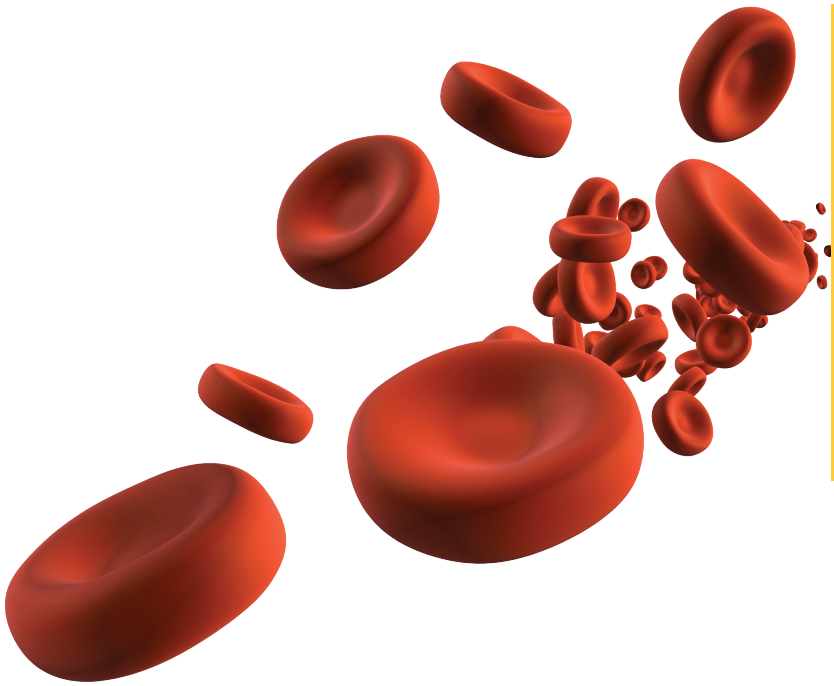
Elderly patients are more at risk of some adverse effects including thromboembolic events, neutropenia and diarrhoea. Extreme caution should be taken in patients with heart failure as there is some evidence that bevacizumab may increase the risk of heart failure.

It is not recommended in patients with recent pulmonary haemorrhage, active hypertension, a history of thromboembolic disease, or in combination with bisphosphonates. Patients should be monitored for signs of central nervous system (CNS) haemorrhage, and caution used in those with untreated CNS metastases.

As bevacizumab may reduce wound healing, discontinue it at least 6-8 weeks before, and until four weeks following major surgery, or until the wound has properly healed. Bevacizumab has not been studied in pregnancy, breastfeeding, or in paediatric patients. It may impair female fertility (possibly reversibly) and is embryotoxic and teratogenic in animals.

Pregnancy is not recommended during treatment because angiogenesis is a process of foetal development. Women should use contraception, and avoid breastfeeding for at least six months following treatment.

Bevacizumab can interact with other medications; it increases the incidence of severe and febrile neutropenia when combined with other myelosuppressive chemotherapy. Care should be exercised when bevacizumab is combined with platinum and taxane based chemotherapy regimens as fatalities have occurred.



It was investigated combined with sunitinib to treat metastatic renal cell carcinoma. However multiple patients developed potentially serious microangiopathic haemolytic anaemia which can be very serious, but all reversed on discontinuation of therapy.

If an initial intravenous infusion of bevacizumab is well tolerated over 90 minutes, it may be reduced to 60 minutes, and again to 30 minutes, for subsequent treatments. Specialist protocols should be referred to for administration and dosing recommendations.

Current data only supports bevacizumab being cost effective, and subsidised by the *Pharmaceutical Benefits Scheme* (PBS), for use in patients with previously untreated metastatic colorectal cancer, who must also receive first-line chemotherapy.

In over half of colorectal cancers, VEGF is overexpressed. Higher amounts of VEGF expression correlates to a worse prognosis. Adding bevacizumab to first-line chemotherapy improves progression-free survival and overall survival. It has been trialled in combination with several first-line treatments including fluorouracil plus oxaliplatin, irinotecan, or capecitabine.

Trials of bevacizumab, in combination with paclitaxel for first-line treatment of locally recurrent or metastatic breast cancer, showed improved progression-free survival (and also overall survival, but this was not statistically significant). It is only indicated as a first-line treatment of metastatic breast cancer, combined with paclitaxel, for patients where anthracycline medications are contraindicated.

Bevacizumab combined with paclitaxel has not been compared with anthracycline protocols, or investigated as second or third-line treatment at this stage. Further research for bevacizumab use in breast cancer is required.

Patients with advanced, metastatic or recurrent non-small cell lung cancer (excluding those with predominantly squamous cell histology) were trialled with bevacizumab in combination with carboplatin and paclitaxel. The bevacizumab treatment group had a statistically significant increase in overall survival compared with patients using chemotherapy alone. Though promising, further research is required to confirm the benefit of bevacizumab in these patients.

Trials combining bevacizumab with interferon alfa-2a monotherapy for advanced and/or metastatic renal cell cancer, achieved statistically significant secondary endpoints of improved progression-free survival and objective tumour response rates.

However, the overall improvement in survival (the primary endpoint) of two months in the bevacizumab group was not statistically significant.

Bevacizumab was studied, in patients with grade four glioma, in combination with irinotecan or with radiotherapy and temozolomide. It improved the six month progression-free survival and objective response rate, and is approved for use in patients with grade four glioma who have relapsed or have disease progression after chemotherapy and other standard therapies.

Investigation into the treatment of epithelial ovarian, fallopian tube, and primary peritoneal cancers showed bevacizumab, in combination with carboplatin plus paclitaxel or gemcitabine, increases progression-free survival.

However, statistically there wasn't a significant increase in overall survival. Bevacizumab's place in therapy for the treatment of these cancers requires more investigation. It has also been trialled for adjuvant colon cancer, but more relapses and deaths due to disease progression were observed. This is not an indication for bevacizumab.

Bevacizumab is a targeted therapy which shows encouraging results in the treatment of many solid tumours. The introduction of new anticancer therapies with new mechanisms of action allows cancer treatment to be more dynamic. The combination of chemotherapy and targeted therapies can improve treatment outcomes.

Bevacizumab is currently only PBS subsidised for metastatic colorectal cancer. Further research is required to demonstrate the benefits of this medication for other indications.

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Nicotine Replacement Therapy

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Smoking is one of the leading causes of mortality and morbidity. Every year over 19,000 Australians die from smoking-related diseases, representing 82% of all drug-related deaths. Smoking can lead to lung cancer, chronic bronchitis, emphysema, and is also a major risk factor for ischaemic heart disease.

Nicotine Replacement Therapy (NRT) aims to reduce the severity of tobacco withdrawal symptoms and increase the likelihood of smoking cessation.

Compared to a placebo, NRT has been shown to increase the chances of people quitting smoking by 1.5-2 times regardless of additional social support. Many different formulations of NRT exist on the market, such as patches, gums, lozenges, sublingual tablets, inhalers, and sprays. Nicotine replacement via the gastrointestinal tract is generally not suitable for NRT as nicotine is subject to first-pass metabolism.

Also, smokers generally prefer the peak effect achieved when nicotine is absorbed directly from either the oral mucosa or the pulmonary system (as in smoking itself) before crossing the blood brain barrier. Cigarettes usually contain 10mg of nicotine or more, with 1-2mg per cigarette being inhaled by the smoker.

This article seeks to describe and compare various formulations of NRT, and discuss the usage of combination NRT to increase the chances of smoking cessation.

Nicotine Gums

Nicotine gums are available in 2mg and 4mg strengths. When the craving starts, the gum is chewed slowly until there is a bitter or tingling taste. The gum is then parked between the cheek and upper gum until the tingling and taste subside. The cycle is repeated until the craving disappears.

People with high nicotine dependence can initially chew up to 6-10 pieces of 4mg gum daily. The dose is then slowly tapered over two months to the 2mg gum, then stopped or tapered after a further four weeks, until ceased. For people with moderate nicotine dependence, 8-12 pieces of 2mg gum are chewed daily, then the dose is slowly tapered according to a regimen, or at the person's discretion.

Nicotine Lozenges

People using nicotine lozenges should allow them to slowly dissolve in the mouth, and avoid chewing or swallowing, as this can reduce the amount of nicotine that is absorbed. Refraining from eating or drinking is also advised during this period.

Those with moderate to high nicotine dependence can start with 4mg lozenges. Those with low to moderate dependence can start with 2mg lozenges.

In both cases, the person should suck one lozenge every 1-2 hours, slowly increasing the amount of time between lozenges during weeks 1 to 24, until they are used only when necessary. Some manufacturers recommend a 12-week program, while Quit® recommends up to nine months.

Seeking medical advice with the intent to completely stop smoking is best, as there is no clear evidence that cutting down, without ever actually quitting, has any health benefits in the long-term.

Sublingual Tablets

The method of sublingual tablet usage is similar to lozenges. They are placed under the tongue and will slowly dissolve over half an hour to release nicotine. One or two sublingual tablets can be used every 1-2 hours, or according to cravings, with a maximum of 40 tablets daily. The dose can be gradually tapered over 8-12 weeks.

Nicotine Inhalers

Nicotine inhalers differ slightly to the other formulations. To use them, the person loads a cartridge and draws on the inhalator mouthpiece when the cravings start, allowing nicotine to be released slowly.

Each cartridge lasts around 40 minutes, and is useful for people who miss the hand-to-mouth movements while smoking. The usual dose is 6-12 inhalation cartridges daily, according to cravings, for 8-12 weeks, and then tapering the dose over subsequent weeks.

Nicotine Patches

Nicotine patches are the only form of NRT subsidised by the *Pharmaceutical Benefits Scheme*. They come in three different strengths to reflect the number of cigarettes smoked in a day. They work by gradually releasing a basal level of nicotine over a 16 or 24 hour period, allowing it to be absorbed via the skin into the bloodstream.

The 24-hour patch is useful for those who have early morning cravings, while the 16-hour patch is preferred if sleep disturbances occur.

If not removed while sleeping, the 16-hour patches will continue to release nicotine from the large reservoir over 24 hours, although plasma levels of nicotine will decline over the last eight hours.

The method of usage involves applying the patch to a clear, hairless part of the body (preferably the upper body or arm), removing it after the specified period of time, and placing a new patch on a different site. Depending on the level of nicotine dependence, a higher dose patch can be applied and then slowly tapered, or stopped abruptly, at about 12 weeks.

Spray Mist

Lastly, the Nicorette Quickmist® spray is a new formulation recently released to the market. It works by discharging a spray of nicotine into the mouth, allowing the nicotine to be absorbed via the oral mucosa into the bloodstream. The dosage is 1-2 sprays every half to one hour for the first six weeks, with the number of sprays used daily during weeks 7-9 slowly reduced to half the average of the first six weeks. Treatment is ceased at week 12, or used only when required.

When deciding between NRT formulations, there are a plethora of factors to consider such as the adverse effects. Irritation of the mouth and throat, as well as sinusitis, are associated with usage of gum, lozenges, sublingual tablets and inhalers, whereas skin irritation and allergies may occur with patches.

Contraindications should also be considered. For example; asthmatic patients should avoid using the inhaler. Pregnancy and lactation also plays an important role in influencing NRT choice. In this case short-acting formulations are favoured over patches, as patches tend to release nicotine over a longer period of time, and can pass through the placenta, affecting the baby.

Another significant factor would be the severity of cravings and withdrawal symptoms. For smokers who have acute cravings, the preferred formulations would be the short-acting formulations such as the inhaler, spray, gum, lozenges, and tablets, as patches cannot be used for relief of acute cravings.

Ultimately, the choice of formulation would depend on the person's preference.

Evidence has suggested that a combination of NRT products can increase the success rate of smoking cessation. As it may be difficult to deliver an adequate dose of nicotine to a highly dependent person using a single formulation, the patch can be used to provide a baseline level of nicotine while supplemented with short-acting formulations for acute cravings.

Editor's Note: *Visit the HPS Pharmacies Knowledge Centre to learn more about Hospital Admission, Abrupt Smoking Cessation, and the Potential for Drug Interaction: http://www.hpspharmacies.com.au/knowledge-centre/*

References

1. Balfour D, Benowitz N, Fagerström K, Kunze M, Keil U. *Diagnosis and treatment of nicotine dependence with emphasis on nicotine replacement therapy*. A status report. Eur Heart J 2000; 21(6): 438–45.
2. Hukkanen J, Jacob P. 3rd ed, Benowitz NL. *Metabolism and disposition kinetics of nicotine*. Pharmacol Rev 2005; 57(1): 79–115.
3. Lancaster T, Stead L, Silagy C, Sowden A. *Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library*. BMJ. 2000 5; 321(7257): 355–8.
4. *Nicorette® (nicotine) Inhalator Australian approved product information*. Ultimo: Johnson & Johnson Pacific. Approved 7 July 2011.
5. *Nicorette® (nicotine) QuickMist Mouth Spray Australian approved pack insert*. Ultimo: Johnson & Johnson Pacific. Approved 23 April 2012.
6. *Nicorette® (nicotine) 16hr Invisipatch Australian approved product information*. Ultimo: Johnson & Johnson Pacific. Approved 4 February 2013.
7. Quit Victoria. *Quit*. Carlton, Australia. Available from < www.quit.org.au/>. Accessed 18 October 2013.
8. Rossi S, editor. *Australian Medicines Handbook 2013*. Adelaide: Australian Medicines Handbook Pty Ltd; 2013. p. 793–5.
9. Stead LF, Perera R, Bullen C, Mant D, Lancaster T. *Nicotine replacement therapy for smoking cessation*. Cochrane Database Syst Rev 2008; CD000146.
10. Zwar N, Richmond R, Borland R, Stillman S, Cunningham M, Litt J. *Smoking cessation guidelines for Australian general practice handbook*. Canberra: Australian Government Department of Health and Ageing; 2004.

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Cytotoxic Drugs and their Safety Considerations

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Safety Considerations

Given the increase in the variety and use of cytotoxic drugs, and also the number of facilities handling them, it is timely to remind and/or update people who come into contact with them on safety considerations, as cytotoxics can be carcinogenic, mutagenic and teratogenic. Some potential adverse effects include foetal loss and malformations, abnormal blood cell count, liver damage, abdominal pain, hair loss, nasal sores, and vomiting.

Similarly, the uptake in use of monoclonal antibodies (MABs) is presently causing some concern over their safety profiles due to their complex and incompletely understood action at a molecular level, and the number of women of childbearing age experiencing chronic low level exposure, such as nursing staff together with other medical professionals. As different MABs have different effects on different human cells, caution should be taken when coming into contact with these agents according to their potential hazards.

Many drugs when used in cancer treatment may be classified as non-toxic, such as the non-cytotoxic antineoplastics everolimus, imatinib, and sunitinib; and the hormonal antineoplastics such as cyproterone and letrozole. These are classified as *Pregnancy Category D* and, as such, care should be taken when handling these medications especially by women of childbearing age or who may be pregnant. Staff should be encouraged to refer to the manufacturer's product information before exposure.

Exposure can occur during: preparation, administration, transportation, storage, handling, waste disposal, and when cleaning up spills; and can involve contact with skin, eye or mucous membranes, inhalation of aerosols or powders, and sharps injuries.

For each of these means of exposure there should be a protocol available detailing what precautions are necessary. All staff who handle cytotoxics must receive training and education appropriate to their level of involvement in these processes. When a high standard of risk control is in place, and adhered to, threats to health are greatly reduced.

All staff handling cytotoxic drugs should be provided with written information on the potential risks of handling these medications and suitable precautions; this advice should also be shared with volunteers and contractors who are not staff. Employers should ensure that only employees who have received and attained the appropriate level of training handle cytotoxic drugs and related waste.

Any health services (including hospitals and medical centres) that are unable to provide the facilities, equipment, and training necessary to provide a cytotoxic drug preparation service should outsource this responsibility to an approved provider, such as HPS Pharmacies.

A minimum set of operating procedures should include:

- Preparation of parenteral treatments,
- Preparation of topical treatments,
- Preparation of oral treatments,
- Operation and maintenance of cleanrooms and ante-rooms used in the production of cytotoxic drugs,
- Operation and maintenance of cytotoxic safety drug cabinets or pharmaceutical isolators used for the production of cytotoxic drugs,
- Receipt and storage of cytotoxic drugs,
- Selection and use of personal protective equipment,
- Cytotoxic waste management,
- Transport of cytotoxic drugs,
- Management of cytotoxic spills, and
- Staff management.

All of these procedures are addressed by HPS Pharmacies when handling cytotoxic drugs and the final product is supplied ready for administration at the health service thereby removing multiple risks of exposure.

Safe Work Practices

Handling techniques can involve the use of both parenteral and non-parenteral preparations and should address:

Preparation

Cytotoxic safety drug cabinets must be used. For parenteral use, glass vials should be avoided if possible due to; their increased risk of breakage and spillage, the care needed to contain excess drug solution and air when priming, and to avoid generation of pressure

differentials that might lead to airborne contamination. Only one drug should be in the cabinet at any one time.

Non-parenteral preparation should also involve the use of a safety cabinet especially when making mixtures or ophthalmic products. Preparation of creams should preferably be avoided due to high risks of contamination.

Again, most health facilities are unable to provide the level of expertise necessary and HPS Pharmacies (as a recognised provider) is able to supply ready prepared medications for immediate use.

Administration

Exposure while administering drugs can occur through handling, spills, splashing, inhalation, and sharps injuries. Risks can be reduced by using closed administration devices, Y infusion lines or Y site adaptors, needleless administration systems, personal protective equipment, as well as having access to a spill kit.

When administering oral tablets and capsules, they must be handled in a manner which; minimises or avoids skin contact, liberation of powdered drug into the air or onto counting trays and other surfaces, and in a manner which avoids chemical cross-contamination. Gloves should be used, equipment cleaned after use, and be purpose dedicated. Tablets should not be crushed or broken.

Cytotoxic Waste

Cytotoxic waste includes any residual material following a patient's treatment; and the materials or equipment associated with the preparation, transport, or administration of the drug therapy. It can include contaminated waste from preparation, IV sets and containers, linen, dressings and bandages, contaminated personal protective equipment, and dose administration aids.

Cytotoxic waste must be disposed of safely to reduce the risk of exposure to waste management workers and contamination of landfill sites. A cytotoxic waste bin should be provided; other contaminated products in addition to those listed above may include nappies, ostomy bags, catheters and the like.

Spills

Spills can involve cytotoxic drugs in all forms; liquid, powder, tablets (whole or broken), or creams. A risk assessment should be performed to identify all areas where there is a likelihood of a cytotoxic spill. Contamination may involve floors, work surfaces, equipment, bedding, clothing, and the patient or their carer/staff member.

A cytotoxic drug spill kit must be available in areas where cytotoxic drugs are used; wherever they are handled, stored, transported, or disposed of. People in the vicinity of a spill should be warned to stay clear and the area isolated. Ancillary workers should only assist in the containment of a spill, until trained personnel are available, by preventing access to the contaminated area if safe to do so.

An emergency shower should also be available in the vicinity where cytotoxics are handled or administered in order to rinse major spills on patients and/or employees to decrease potential harm.

Spill management strategies should be developed by all employers and involve the use of a cytotoxic spills register.

In conclusion, it can be seen that cytotoxic drugs require a great deal of attention to safety during production, preparation, handling and disposal. Using an approved provider such as HPS Pharmacies can greatly reduce exposure risk, as the cytotoxics are supplied already prepared thus removing staff involvement in production, preparation, and some handling procedures.

All staff involved in the supply of cytotoxic drugs from the doctor down to any ancillary workers should be provided with training relevant to their level of exposure, and protocols put in place to ensure that their safety is paramount.

If cytotoxics are treated with respect, ordered from approved providers, and administered correctly, there is little likelihood of any unwanted exposure, and staff can feel entirely confident about their involvement in patient care when using these drugs.

References

1. Bratt-Wyton R, Neilson JR, Kahlon R. *Procedure for Prescribing, Safe Handling and Administration of Cytotoxic Therapy and Monoclonal Antibodies*. 3rd ed. Dudley: Dudley Group of Hospitals NHS Trust; 2010.

2. Cytotoxics Work Group. *Safe Handling of Cytotoxic Drugs and Related Wastes: Guidelines for South Australian Health Services 2012*. Adelaide: SA Health; 2012.

3. Rossi S, editor. *Australian Medicines Handbook 2013*. Adelaide: Australian Medicines Handbook Pty Ltd; 2013. p. 532ff.

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Chemotherapy in Pregnancy

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Cancer is the second leading cause of death for women during the reproductive years. It complicates 1 in 1,000 pregnancies, and the incidence is expected to rise with the increasing age of child bearing. There are more than 3,500 incidences annually in the United States. The most common types of cancers diagnosed in pregnancy are those that are seen in non-pregnant women of reproductive age, for example; breast and cervical cancers, melanoma and lymphoma cancers.

Maternal-foetal conflict occurs when it comes to treating pregnant women with cancer. Life-saving treatments for the mother may pose life-threatening effects to the developing foetus. On the other hand, the "watch and wait" measure of delaying treatment until after delivery may put the mother at risk, especially in aggressive malignancies (e.g. acute lymphoblastic leukaemia). The timing to give appropriate treatment is critical and decisions should be case-specific.

Many cancers discovered during pregnancy are at an advanced stage due to delayed diagnosis. This is because non-specific signs and symptoms (e.g. weakness, fatigue and dyspnoea) are often mistakenly related to gestation. Physiological changes during pregnancy may mask early signs of malignancies, such as increased hormone levels causing breast enlargement making small lumps difficult to notice, or signs of melanoma being masked by hyperpigmentation in pregnancy. In contrast, more cervical cancers are detected at early stages through routine antenatal check-ups.

The teratogenicity of any drug depends on gestational age at exposure, dose administered, characteristics affecting placental transfer, lipid solubility, molecular weight, and binding to plasma proteins. Most chemotherapeutic agents have a molecular weight less than 600kDa and are able to cross the placenta to reach embryonic circulation, unless they are highly bound to plasma proteins.

Chemotherapeutic agents generally fall into category C, D, or X of the Australian Drug Evaluation Committee (ADEC) Pregnancy Categories:

- **C category:** May cause harmful effects on the human foetus without causing malformations. These effects may be reversible.
- **D category:** Have caused an increased incidence of human foetal malformations or irreversible damage but the benefit justifies the potential risk to the foetus.
- **X category:** Have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

Most of this information is obtained from animal studies and it is difficult to extrapolate the data to humans. Furthermore, therapeutic doses used in humans are generally lower than the minimum teratogenic dose found in animal models.

The impact of chemotherapy on foetal health depends on three key factors:

1. Maternal physiological changes associated with pregnancy;
2. Developmental stage at which the foetus is exposed to the drug; and
3. Type, duration, and dose of the drug.

Maternal physiological changes are not frequently studied and currently there are no pharmacokinetic studies in pregnant women available. A pregnant woman may have lower gastrointestinal motility, fluid retention (50% increase in plasma volume), lower concentration of plasma albumin, higher hepatic oxidation rate, and higher renal clearance. Therefore, in theory, the active drug concentration in pregnant women is lower than non-pregnant women and this

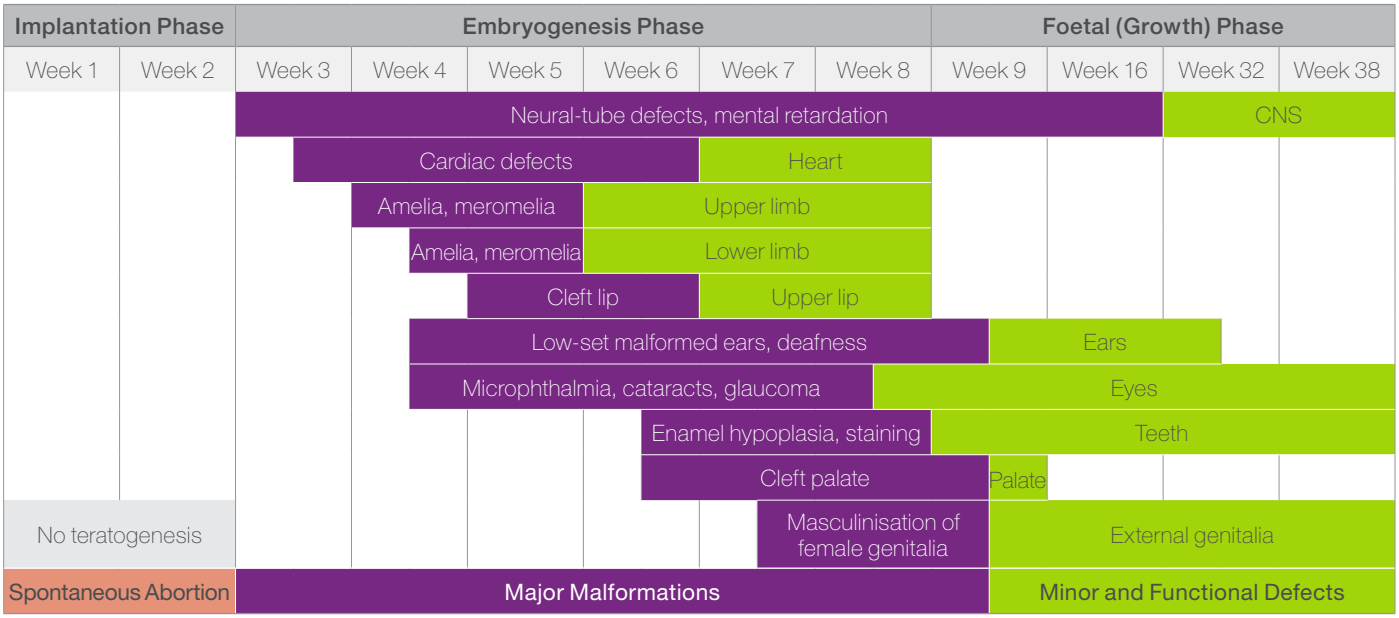

Table 1. Phases of foetal development and teratogenicity.

may impact the efficacy of treatment. However, it is not a routine practice to increase chemotherapy doses in pregnant women due to lack of evidence.

There are three important phases of foetal development; implantation, embryogenesis/organogenesis, and foetal or growth periods (see Table 1). The first two weeks of pregnancy (the implantation period) is not susceptible to teratogenesis.

Use of chemotherapy during the first trimester, especially gestational weeks 2-8, increases the risk of spontaneous abortion, foetal death, and major malformations. Malformations may reflect the gestational age at exposure: the heart, neural tube, and limbs are affected earlier than the palate and ear. A review of 139 cases of first trimester exposure to chemotherapy quantified the risk of malformation after: single agent exposure at 17% (or 6% if antifolate is excluded), and 25% for combination agents (Doll, 1998).

This showed that the risk of malformation increases with combination agents and that antifolate possesses a higher risk of malformation compared to other drugs.

Another study showed that exposure during the second and third trimesters increases the risk of foetal or neonatal death (6%), intrauterine growth restriction (7%), low birth weight/premature delivery (5%), and neonatal myelosuppression (4%). Maternal nutritional deficiencies, caused by tumour or chemotherapy-induced anorexia, can also affect foetal growth and birth weight. Impairment in learning, behaviour, or haematological abnormalities have not been documented in long term studies (Cardonick, 2004).

Methotrexate, an antifolate, can cause similar malformation to "aminopterin syndrome" if doses over 10mg/week are given in the first trimester. Aminopterin syndrome is cranial dysostosis with delayed ossification, hypertelorism, wide nasal bridge, micrognathia and ear anomalies. Exposure in later trimesters is not associated with significant malformation.

Retrospective reviews of 12 pregnant women given cyclophosphamide, methotrexate and fluorouracil (CMF) showed 11 had treatment during the second and third trimesters with no malformation reported. Only one woman had treatment during the first trimester, resulting in spontaneous abortion after cycle one of CMF (Ring, 2005).

Anthracyclines are much safer, especially if not administered during the first trimester and in doses less than 70mg/m^2 for doxorubicin. Epirubicin should be avoided due to its lipophilic nature and increased placental transfer. Idarubicin has been linked to malformation of the heart and coronary vessels in human embryos.

Some of the 'newer' chemotherapy agents display high activity against breast cancer, for example paclitaxel, docetaxel, vinorelbine, trastuzumab and lapatinib. However, their use in human pregnancy has been limited and rarely reported. Nine reports document the use of paclitaxel in second and third trimester of gestation.

Paclitaxel was administered as a single agent in two out of the nine cases, and in combination with other chemotherapy (cisplatin, carboplatin, trastuzumab, epirubicin, and AC [doxorubicin/cyclophosphamide] protocol) for the rest.

No malformations were reported (Mir, 2008). Of six reports documenting the use of trastuzumab, three were found to be initiated before conception. Anhydramnios was reported in three cases, and was found to be reversible, in one case after trastuzumab withdrawal (Mir, 2008).

In conclusion, chemotherapy in the first trimester is associated with an increased rate of spontaneous abortion and major birth defects and should be avoided. Ultimately, patients should be involved in all decision-making and need to be counselled regarding the stage of the disease, urgency of initiating treatment, treatment options available, and the potential effect or outcome of treatment to mother and her developing foetus.

References for this article can be found in the online version published in the HPS Pharmacies Knowledge Centre.

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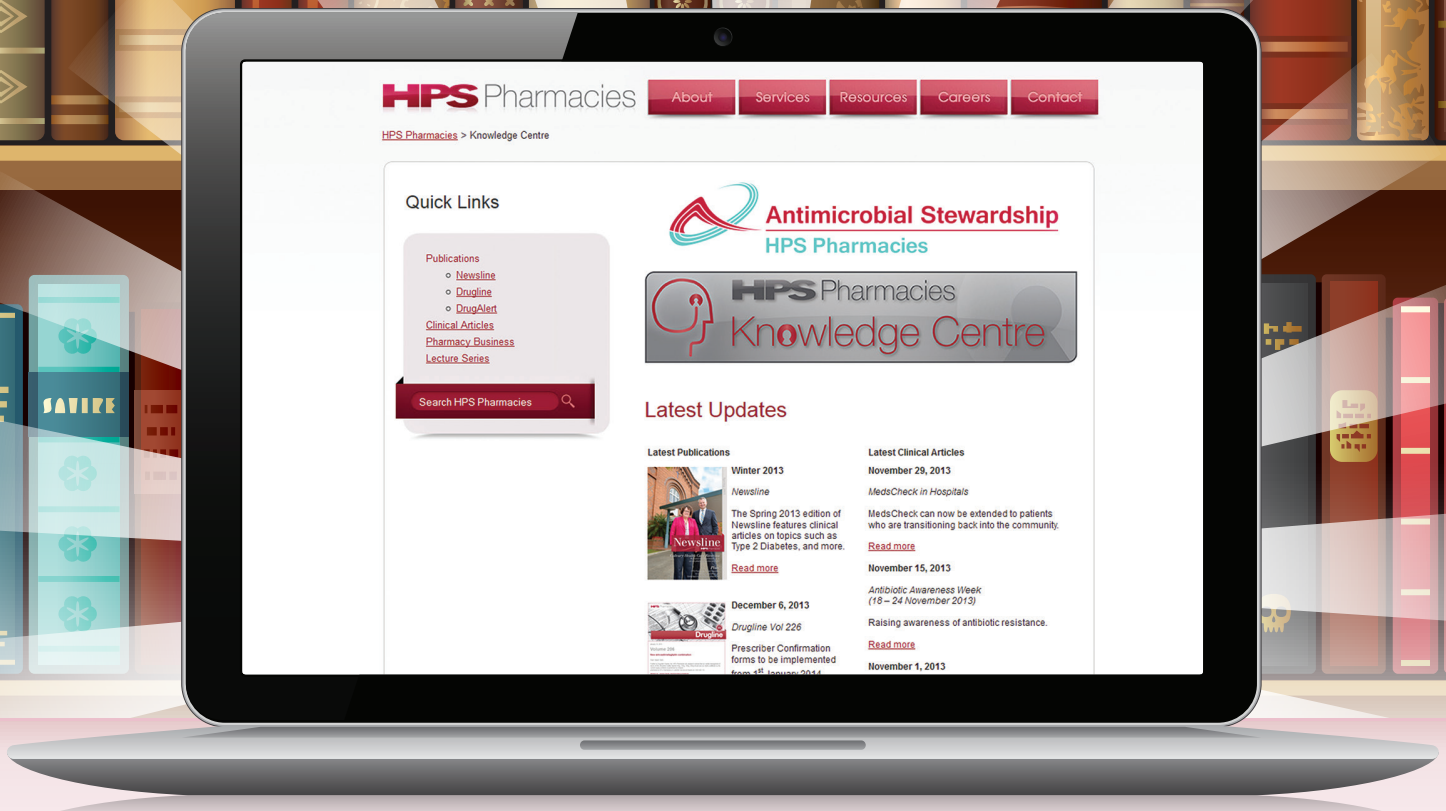

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