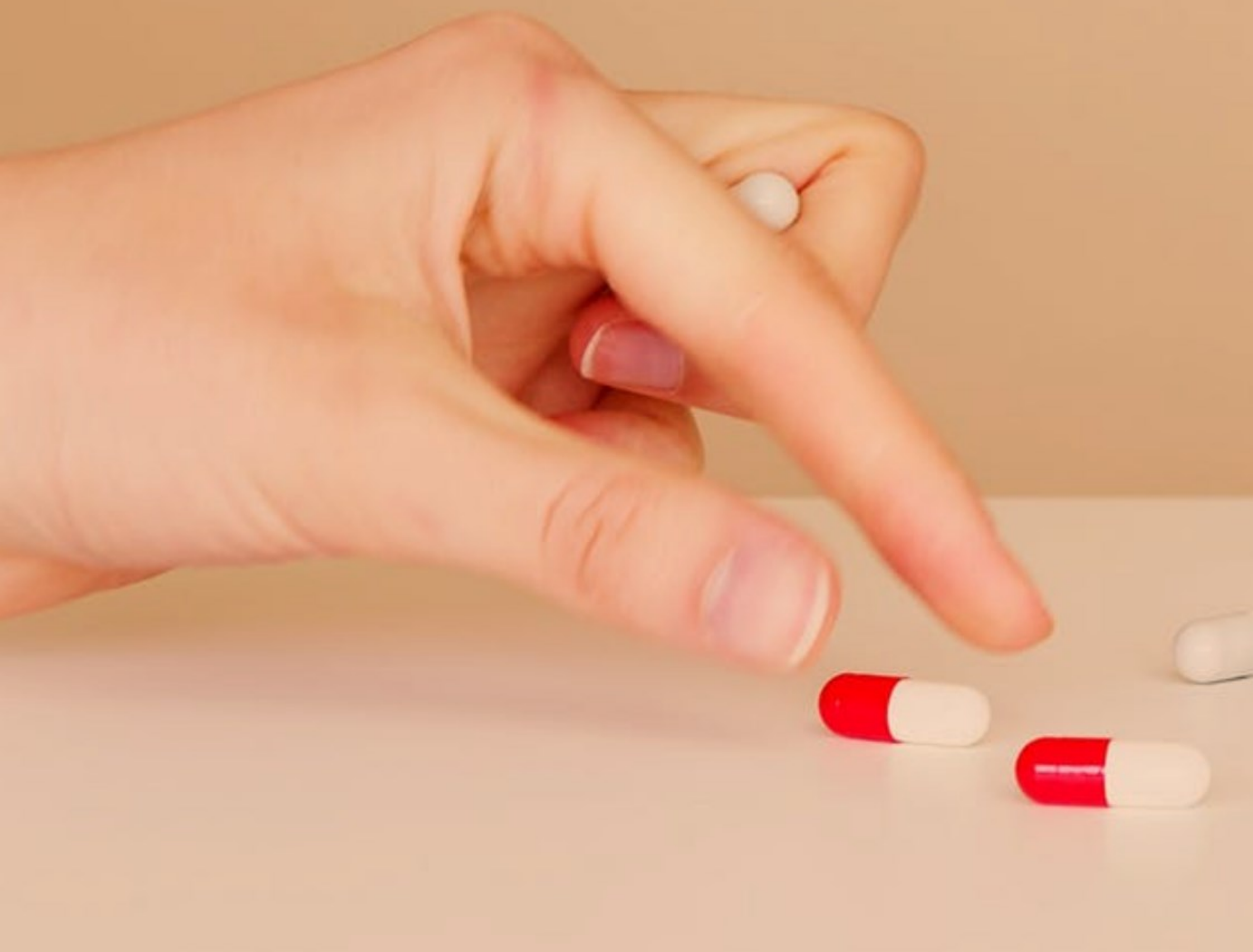


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A white ceramic jar with a white lid, sitting on a reflective surface. The word "WRITERS" is printed in red capital letters on the front of the jar.

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The Gist of Genetic Screening

By: Maja MacNeil Soltysiak

Our knowledge of the human genome and its possible variants has increased astronomically over the past few decades, especially thanks to technological advancements. Discrepancies and mutations in our genomes are now known to cause genetic diseases, such as cystic fibrosis and Down's syndrome. And since the 1960s, we have been able to test individuals for a predisposition to inherit or pass on such diseases with the use of genetic screening.

Genetic screening can be understood to be the testing of asymptomatic individuals to assess the risk of said individual having a predisposition for an inherited disease, of passing along such diseases to their potential children, and to detect the risk of a fetus or baby being affected by such diseases[1].

Genetic screening is often confused and used interchangeably with genetic testing, however, the two procedures actually differ in that the former is the testing of asymptomatic individuals, while the latter tests symptomatic individuals[1]. Genetic screening can also be understood to be a systematic evaluation (a public health program) originally aimed at the improvement of population health, with the results of screening aiding in preventing disease, starting treatments early, and allowing greater opportunities for family planning[1].

The practice of genetic screening first began in the 1960s with the use of blood-spot screening[1] to test newborn babies for a genetic condition called phenylketonuria (PKU)[2]. Early detection of PKU allowed healthcare practitioners to promptly place affected babies on a specific diet that would prevent neurological effects from the condition. This type of screening has since developed dramatically and can now test for multiple groups of potentially deadly diseases including metabolic diseases, endocrine diseases, and sickle cell diseases, cystic fibrosis, severe combined immune deficiency (SCID), spinal muscular atrophy (SMA), and critical

congenital heart disease (CCHD)[3].

Newborn screening, conducted on babies promptly after birth, is only one of three major types of genetic screening[1]. Another is pre-conception screening, conducted on individuals prior to having children in order to predict whether or not they are at risk of passing on recessive conditions to potential offspring[1]. The last is prenatal screening, conducted during pregnancy. It assesses the risk of a fetus having certain congenital conditions[2].

In 1968, Wilson and Jungner of the World Health Organization worked to develop the first criteria for screening. This included that the screened disease must be a significant health issue and must be treatable[4]. While Wilson and Jungner's proposal was accepted and followed for many years, the list was revised by WHO in 2008 to accommodate for advances in our knowledge and technology, given the genomic revolution[4]. Notably, the revision added the recognition of equity and informed consent.

Genetic screening is widely supported for its undeniable success in saving children's lives and reducing disease[5]. These benefits are why genetic screening is considered one of the top ten greatest public health achievements[5]. It is also argued that genetic screening has become highly important to reproductive autonomy[6]. With autonomy in medical decision making, namely, the right to self-determination, individuals are entitled to be able to make the most informed choice possible. Because genetic screening increases how informed one is about their reproductive journey, it therefore promotes patient autonomy.

However, genetic screening is often criticized on many social and ethical points. First, screening results are not 100% accurate. False positive and false negative results occur and can create false consolation or unnecessary stress[6]. Second, there are social pressures for individuals to undergo genetic screening.

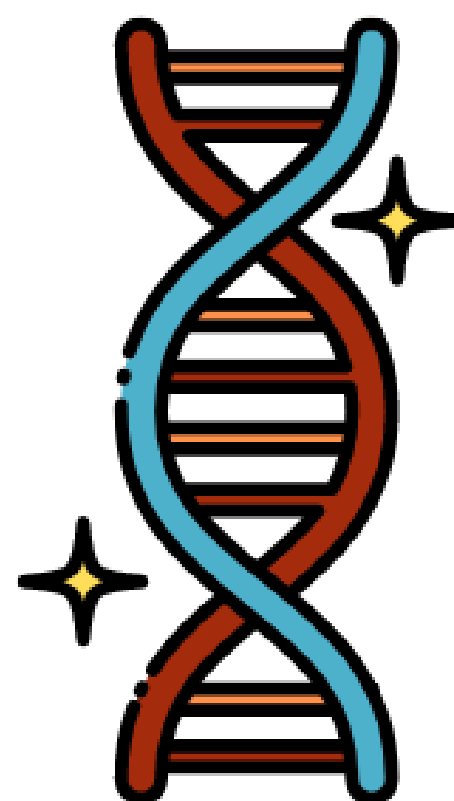
Some think that opting out of screening is irresponsible because by participating in screening, an individual may be able to prevent or help a medical condition that their offspring may suffer from. Also, screening programs are claimed to be offered for the benefit of society as a whole and opting out could result in unnecessary burdens on our health systems[6]. Third, given a fear of malpractice or negligence lawsuits, medical practitioners may overload individuals with information about screening. Information sessions may also be interpreted as healthcare workers pressuring patients towards certain screening options or pregnancy termination[6]. These both may result in patient confusion and improper decision making. Fourth, the common eugenics critique of genetic screening argues that such risk assessment not only leads to the perpetuation and further stigmatization of disabilities and diseases, but also lower birth rates of individuals with certain conditions, which may result in a decrease of resources and supports for said conditions[6].

Do the pros of genetic screening outweigh the cons? Are the above ethical concerns solvable? New technologies such as whole genome sequencing offer incredible potential for revealing and understanding genetic variations[5]. And already, technologies such as non-invasive prenatal testing (NIPT) (in use since 2011) have dramatically improved the accuracy of genetic screening and reduced the need for invasive diagnostic procedures[6]. While our current understanding of the genome is still limited, our knowledge and technological capabilities will only progress, and with it, our ability for disease risk detection with genetic screening. And as screening technologies become more powerful and more accessible, the associated ethical considerations will evolve too. Going forward, then, it is important that we ensure the needs of individuals and society are being respected and considered, that ethical and equity considerations are valued, and that technologies are not abused or used prematurely.

Drug interactions also have the potential to affect the prognosis of AHCT for HRLs.

Anti-HIV medications used in cART can affect drug metabolism quite significantly. One of these medications is the protease inhibitor ritonavir. Ritonavir is a P-glycoprotein inhibitor, as well as a potent inducer of the CYP3A4 drug-metabolizing enzyme that approximately 50% of drugs are a substrate for[1,10]. Extensive consideration is thus required when administering antiretroviral drugs such as ritonavir, as many have the potential to alter the desired plasma concentrations of other administered drugs[11].

Alvarnas et al. identified that drug regimens such as those with etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab yield progression-free survival (PFS) rates of 73-90% in patients with HIV-associated NHL. The success of treatments is generally dependent on various patient factors such as treatment history, patient histology, and the efficacy of past treatments. Thus, whether a patient's disease state is relapsed, or refractory must also be considered in prognoses[1]. Multiple studies have seen that the PFS and overall survival (OS) rates were uninfluenced by patient HIV stage, CD4 cell count, or viral load [5]. This was likely due to cART controlling HIV progression[5].



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Telehealth in 2020 and Going Forward

By: Caleb Chan

I like to be outdoors. Hiking, camping, and canoeing are staples of my childhood. Being sick is also a staple—so being outdoors while sick is my recurring motif. Even now I remember lying supine with a raging fever on a canoe trip, hearing distant laughter in my nauseous haze. With the nearest doctor a day's canoe away, my instructors and I hoped—and soon believed—my condition as mere fever. I was later told by my doctor that I had pneumonia.

With the ubiquity of smartphones, computers, internet and mobile data, telehealth—the use of technology to provide medical care[1]—has taken over the examination room; I can see my doctor in Toronto on a canoe trip around Vancouver Island.

But the COVID-19 pandemic swept the world, and my excitement in the potential of telehealth was no longer personal. The American Medical Association estimates that 75% of doctors have begun to use telehealth in response to distancing measures to reduce non-critical medical visits [2]. The stubborn spread of the virus has also pressured hospitals worldwide and overwhelmed healthcare systems [3]. To lessen this load, telehealth has thus arisen as a vital means of assessment and care for patients [1].

A systematic study by Monaghesh and Hajizadeh (2020), evaluating the usage of telehealth in the pandemic, presents telehealth as “strongly recommended” to curtail spread of the virus [1]. Unlike physically visiting an examination room, telehealth is conducted remotely in the safety of the patients, reducing exposure to other patients and healthcare workers to hinder contact [3].

There are three main ways in which telehealth is used to directly care for the patient: to screen for possible COVID-19 infection, contact tracing, and to monitor infected patients [4].

Screening for COVID-19 is conducted through online self-assessments or synchronous phone

examinations to determine if the patient is infected [1].

I visited Ontario's COVID-19 website and took a self-assessment that asked for my age, postal code, symptoms, and level of exposure with others to determine the likelihood of my infection [5]. I was judged virus-free, but if the algorithm had deemed me as potentially infected, it would urge me to get tested for the virus and display testing centres closest to me. [5].

Contact tracing is the process of identifying infected patients and those they may have physically interacted with to prevent the spread of the virus [6]. Telehealth, mainly through phone calling, has been the primary means of contact tracing [6]. Suppose I was infected and began showing symptoms on Monday. A public health official would call me and ask who I had contacted in the past two days—up to Saturday—and would then ask these people to self-monitor for symptoms of possible infection [7].

To monitor infected patients during self-isolation, the use of telehealth to mediate doctor-patient communications has become mainstream [1]. The American health insurance program, Medicare, was promptly expanded to cover telehealth options covered by insurance; prior to the pandemic, telehealth coverage was restricted for rural patients [8]. Globally, patients can be monitored and triaged using synchronous video conferencing to determine the severity of their symptoms, with respiratory symptoms particularly observed using this method [9]. Specialized devices, in addition to video conferencing, are also used—such as sensors to detect blood rate, pressure or sugar—to transfer medical data between patients and doctors [10].

Telehealth is also used to indirectly care for the patient. In Wuhan, China, a study compared in-person versus distant learning methods when teaching nurses to work during the pandemic [11].

The electronic, distant training cohort scored similarly in examinations to the in-person cohort and reported higher satisfaction levels in comparison to the in-person cohort [11]. Around China, mental health surveys were conducted using popular social media apps, such as WeChat, Weibo, and TikTok, to aid health officials in determining where to allocate funding for mental health resources [12].

The sudden transition to telehealth, however, brings challenges that must be solved if telehealth is to be sustainable post-pandemically. The technical infrastructure hastily assembled for the patient care in the pandemic—largely ad hoc with personal equipment and software—is not viable as a long-term solution to ensure proper regulation and patient confidentiality [13]. Health networks will thus need to construct in-house telehealth networks and systems to streamline new methods of patient-centred care and staff organization [13]. Educational material for healthcare workers will need to be modified to teach staff how to effectively care for patients in a virtual setting [14].

And this virtual setting has inherent limitations: In addition to a doctor's inability to touch the patient and operate equipment on the patient, doctor-patient communication is restrained [15]. In a study on telehealth-mediated adolescent epilepsy care, neurologists observed that teenage patients refrained from sharing sensitive information about their mood and lifestyle when video conferencing for fear of a parent or sibling overhearing them [15].

The pandemic has heralded a new epoch in healthcare: telehealth. The once futuristic possibility of virtual healthcare has become widespread and is projected to extend beyond pandemic novelty [2]. Telehealth allows health information to be circulated efficiently and healthcare to be conducted safely, but its viability depends on the response of doctor, patient, and institution if telehealth is to mature and flourish.



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Prostate Cancer: Pathophysiology and Pharmacotherapy

By: Ziyi Li

Introduction

Prostate cancer is the leading cancer diagnosis and the second leading cause of cancer deaths in men[1]. In 2020, it is estimated to account for 1,414,259, approximately 7.3%, of all new cancer diagnoses and 374,304 deaths, approximately 3.8%, of all cancer death around the world[2]. Though statistics from the World Health Organization have shown that the incidence and mortality of prostate cancer in Asia and Europe are drastically higher than it is in North America, the situation remains serious in Canada. The 2020 projected estimates study of the Canadian Cancer Statistics Advisory Committee reported that 23,300 men will be diagnosed with prostate cancer meanwhile 4,200 men will die from prostate cancer in Canada[3]. Fortunately, over the past thirty years, the risk factors, molecular mechanism, clinical diagnosis as well as pharmacotherapies of prostate cancer have been continuously studied by scientists from all over the world. With some significant breakthroughs made, the overall death due to prostate cancer is on the decline[1].

Pathophysiology of Prostate Cancer: Cellular Progression

Testicular androgens are essential for the development and functioning of the prostate through the entire life of males. In the fetus, a high level of testosterone is produced for the formation of male genital organs. With 5 α -reductase in prostate cells, testosterone is converted to 5 α -dihydrotestosterone (DHT) which promotes the growth and survival of prostate cells. This conversion is especially important during the prepubertal and pubertal period, in which the prostate continuously grow to reach its adult size[4]. After fully grown, prostate cell proliferation and death are balanced. The balance is especially important in maintaining a normal prostate physiology. Either an increased proliferation or a decreased death caused by various

enzymatic and genetic molecular changes promotes prostate cancer development.

While the loss of tumor suppressor genes including phosphatase and the tensin homolog (PTEN) and NK3 Homeobox1 (NKX3.1) can result in uncontrolled proliferation of cells, the fusion of transmembrane Serine Protease 2 and the ETS-related gene (TMPRSS2-ERG) disrupts androgen receptor signaling pathways in prostate cells[5]. With the uncontrollable expansion of a single precursor cell with mutations in tumor suppressor genes or epigenetic changes in androgen sensitivity, normal prostate epithelium undergoes a low-grade or high-grade prostate intraepithelial neoplasia (PIN), which, with further accumulation of mutations, can proceed to prostate adenocarcinoma. Prostate adenocarcinoma, also called metastatic prostate cancer, is initially indolent[4,5]. However, continuous acquirement of mutations in tumor suppressor genes and enzymatic trigger the transformation of the localized and small prostate tumor into invasive prostate adenocarcinoma which can travel along with blood circulation and metastasize to different parts of the body.

Pharmacotherapy of Prostate Cancer: Present and Future

Currently, available treatment options for prostate cancer include surgery, radiation, cryosurgery (cryotherapy), hormone therapy, chemotherapy, vaccine treatment, and bone-directed treatment, etc[7]. The initial therapies to prostate cancer usually aim to remove or destroy cancerous cells in the prostate using prostatectomy and/or radiation, which, unfortunately, cannot completely cure patients and usually end up with a recurrence of cancer. A widely adopted first-line of treatment of prostate cancer is a hormone therapy named Androgen Deprivation Therapy (ADT).

ADT can be applied if the patient has or is at high risk of failing or recurring after surgery or radiation therapy, or if the patient needs a more effective way of shrinking prostate tumor even before radiation therapy[9].

Two possible options in ADT are surgical castration and medical castration. Surgical castration surgically removes the main site of testosterone synthesis, testicles, which is effective to limit most prostate cancers to progress for a while. Medical castration, on the other hand, is to limit prostate tumor growth by lowering testosterone levels using drugs. ADT drugs can be classified into Luteinizing hormone-releasing hormone agonist (Leuprolide, Goserelin, Triptorelin, etc.) or antagonist (Degarelix, Relugolix) that act on testis to lower testosterone production, androgen synthesis blocker (Abiraterone, Ketoconazole) that act on the adrenal gland to block androgen synthesis and anti-androgens (Flutamide, Bicalutamide, Nilutamide) that act on androgen receptors of prostate cancer cells[8,9]. As the tumor growth is initially androgen-dependent, androgen ablation can effectively lead to tumor regression in early-stage progressive prostate cancer.

Despite the diverse range of existing options in ADT, responses of prostate tumors to therapies show the interindividual difference due to the inter-tumoral heterogeneity of prostate cancer. To differentiate patients with intermediate-risk, a genomic risk of prostate cancer progression and recurrence, as well as design novel effective therapies, researchers at the University of Toronto proposed to identify prostate-cancer-inducing genomic pathways that can be applied in defining subtypes of localized prostate cancer[10]. After conducting whole-genome sequencing, RNA analysis, and methylation analysis of more than 200 localized prostate tumors, the specific genomic profiles of localized prostate tumors were found

to include numerous recurrent non-coding aberrations including DNA methylation events, large-scale gene rearrangement, altered inversion repressed transcription, and frequent local hypermutation. Based on results, researchers suggested that it might be more beneficial to give intense treatment such as widespread genotoxic chemotherapy to patients with genomic profiles at high risk of developing and recurring localized prostate cancer.

The importance of genomic risk in prostate cancer, pieced together by researchers, provides an insight into future prostate cancer therapies. Current determinants of therapy depend on the stage of prostate cancer development predicted by clinical tests including Prostate Specific Androgen (PSA) blood tests, CT scans, and bone scans[11]. Surgery, radiation, and Androgen Deprivation Therapy are usually the first line of treatment for localized prostate cancer. Though effective at the early stage of development, these therapies cannot completely and permanently stop prostate cancer. The progression of prostate cancer from androgen-dependent to androgen-independent is inevitable. Chemotherapy is usually applied at the point of androgen-independent prostate cancer (AIPC), also called castration-resistant prostate cancer (CRPC), which is usually lethal. Thus, in the future, the determination of individual susceptibility to aggressive progression, recurrence, and death of prostate cancer may be important in designing personalized therapy that best fit the individual.

Over the past decades, numerous studies of prostate cancer conducted around the world pictured a much better pathophysiological mechanism and developed a range of therapy options for prostate cancer. As stated by Dr. Robert Bristow, a prostate cancer researcher at the University of Toronto, that in the near future, more genetic architecture-specific pharmacotherapy will appear and give hope to curing prostate cancer[12].



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Off-Label Use of Drugs for Various Pathologies

By: Eric Jihun Kim

Off-label use of drugs refers to use of drugs for the purpose other than what is indicated on the drug label[1]. A label of a drug indicates overall profile of the drug submitted by the manufacturer, including doses, safety, specific indications, and directions of use, which is then approved by Health Canada for sale in Canada[2]. Drugs are said to be used “off-label” if they are used for treatment of illness or disease outside of authorized use, population, dose, or route of administration as indicated[1]. Several reasons for “off-label” use of drugs include prescribing a drug for children, elderly, or pregnant women who are not usually included in clinical trials, for treating symptoms similar to those in the label indication, exhaustion of available on-label use options of the drug, treatment of rare diseases, or novel uses of the drug that are not yet authorized by Health Canada[1].

One of the common drugs being used “off-label” is sildenafil, often known as Viagra. Sildenafil is approved by US Food and Drug Administration to treat male erectile dysfunction and World Health Organization Group I pulmonary hypertension traditionally due to its ability to relax vascular smooth muscle via inhibition of phosphodiesterase-5 (PDE5) followed by accumulation of cGMP[3]. However, it is also known to be occasionally used by patients to treat conditions such as female sexual arousal disorder, Raynaud phenomenon referred as spasm of the arteries due to exposure to cold, and altitude-induced hypoxemia[3,4].

Another drug that is often used outside of labelled instruction is minoxidil. Being discovered in 1970 as a potential vasodilator, minoxidil was found to cause hypertrichosis with chronic use[5].

After the discovery of side effect such as hirsutism in women, the drug was

turned into topical form that was marketed under the name Rogaine in 1988 for treating androgenetic alopecia also known as male-pattern baldness as well as female hair thinning by promoting hair growth[5,6]. The product for both male and female has been enabled for purchase without prescription in 1996, and minoxidil is currently available in multiple formulations including a 2% solution, a 5% solution, and a 5% foam[5]. Even though the exact mechanism of minoxidil in promoting hair growth is not clear, it is thought to induce cutaneous blood flow to the scalp as well as activate potassium channels in order to switch hair follicles from resting telogen phase to active anagen phase[5]. However, a comprehensive review involving clinical trials, case reports, and case series reports that topical minoxidil is also used for other types of hair loss[5]. This includes immune-mediated alopecia areata, scarring alopecia characterized by destruction of hair follicle and formation of fibrous scar tissue, eyebrow hypotrichosis referred as loss of eyebrows due to trauma, medical or surgical treatment, systemic diseases, etc., and monilethrix, which is a genetic disease that causes fragile hair, thinning of hair shaft, and keratosis pilaris[5]. These conditions are overall known to have less to no effective cure in remission[5].

Modafinil is another example of drug that is often used “off-label.” As a psychostimulant, modafinil has been used to treat sleepiness due to narcolepsy, obstructive sleep apnea/hypopnea syndrome, or shift work sleep disorder, potentially via activation of orexin neurons in the lateral hypothalamus, activation of central alpha 1-adrenergic receptor, increasing excitatory glutamatergic signaling by reducing GABA transmission, and inhibition of dopamine reuptake by dopamine transporter[7,8].

Other than the indicated use of inducing wakefulness, modafinil is also known to be used in several other conditions including depression, memory enhancement, Alzheimer's disease, and fatigue due to disease, battle, etc.[7].

It is thought that off-label drug use is becoming more common. For example, about 11% of drugs are prescribed for conditions that are not approved by Health Canada and 75% of drugs are used off-label in children[1,9]. Also, off-label use of modafinil from 2002 to 2009 increased more than 15-fold according to the National Ambulatory Medical Care Survey and off-label use of antipsychotics from 1995 to 2008 increased from 4.4 million to 9 million in terms of treatment-related visits[10]. While more people are using drugs for conditions that are not indicated on the label, there are several factors that we also need to consider when using drugs for these purposes.

One of the important things to consider is the extent of efficacy of the drugs when used off-label. For example, there are discrepancies in studies regarding the effectiveness of sildenafil in female sexual arousal disorder, such as a study reporting that sildenafil was effective in increasing vaginal vasocongestion and sexual arousal in healthy premenopausal women that is opposed by a study reporting that no clear evidence of sildenafil in improving sexual response was seen in women with sexual arousal disorder[11,12].

Also, a review in 2019 showed that while there was more supportive evidence of topical minoxidil in treating eyebrow hypotrichosis and monilethrix, its effectiveness in treating alopecia areata and scarring alopecia was still not clear[5]. Therefore, future studies would need to focus on accumulation of more concise and conclusive evidence of effectiveness of off-label use with more clinical studies.

Another issue is side effects related to using the drugs such as prolonged erection, headaches, dyspepsia, and change in color vision due to administration of sildenafil[3], dizziness, irregular heartbeat, and unwanted growth of body hair due to administration of minoxidil[6], and overdose response, agitation, and anxiety due to administration of modafinil[7,8]. Since there is a higher possibility that patients would administer off-label drugs outside of indicated dose on the label, these kinds of symptoms are more likely to be seen in off-label drug use.

Overall, more people are beginning to use drugs for treating symptoms that are not approved by Health Canada, and this could become serious side effects and potentially social issue if not properly supervised by pharmacists or clinicians. Therefore, thorough examination of body conditions, diets and drugs currently being taken, and regular report of the changes in the body would need to be consulted with pharmacists when taking drugs off-label.



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Current and Prospective Pharmacotherapies for Type 2 Diabetes Mellitus

By: Maggie Yang

Diabetes is a serious health issue of constant research and discussion because of its increasing prevalence worldwide. Diabetes has caused about 10% of death between 2004 to 2008 in Canada [1]. Recently, diabetes mellitus is ranked as the 9th leading cause of death globally in 2019, due to a 70% increase in death compared with 2000 [2]. In this article, I focus on oral medications for Type 2 diabetes mellitus (T2DM), as it is much more frequent in developed countries such as Canada, representing about 90% of all diabetes cases [3]. I will examine two widely used oral medications available for managing T2DM: metformin and sulfonylurea. I will go over their mechanisms, advantages, and disadvantages.

T2DM is a chronic disease marked by hyperglycemia caused by insulin resistance and decreased insulin secretion. Common symptoms include extreme thirst, fatigue, weight changes, blurred vision [4]. If the disease progresses without intervention, patients can experience complications including nephropathy, retinopathy, cardiovascular diseases, and peripheral neuropathy [5]. Retinopathy can lead to blindness, affecting the patient's quality of life significantly [5]. Other complications, such as cardiovascular disease, can be fatal. Therefore, treatments, which lower glucose concentrations, are essential to ensure that complications do not arise.

Metformin is regarded as the first line of oral medicine for the management of T2DM. In a recent meta-analysis of clinical trials of 11 oral antidiabetic drugs, metformin was found to be one of the most effective antidiabetic drugs [6]. The study suggested that metformin should be used when there are no contraindications or intolerance [6]. Contraindications of metformin include renal impairments;

however, metformin is safe for mild to moderate kidney disease.

Metformin is a biguanide that lowers glucose concentration by decreasing glucose synthesis in liver cells and increasing insulin sensitivity. However, the molecular mechanisms of metformin are not thoroughly studied despite its wide use for treatment [7]. One proposed mechanism involves activation of adenosine monophosphate-activated protein kinase (AMPK) to decrease gluconeogenesis [7]. AMPK is activated when AMP concentration is high, and respond to low energy in the cell by activating catabolic processes while simultaneously inactivates anabolic processes to increase ATP concentration [8]. Shaw et al. suggest that metformin may activate AMPK through LKB1, a tumour suppressor upstream of AMPK [7]. Loss of LKB1 resulted in a reduction of AMPK activation, hyperglycemia, increased gluconeogenesis and lipogenesis, suggesting that activated LKB1 suppresses anabolic pathways in liver cells [8]. They examined the effect of metformin in mouse liver cells in the absence of functional LKB1 protein and observed that blood glucose was not lowered [8]. In addition, metformin may act through AMPK-independent pathways, such as by reducing cAMP (cyclic AMP) level and PKA (protein kinase A) activation [7].

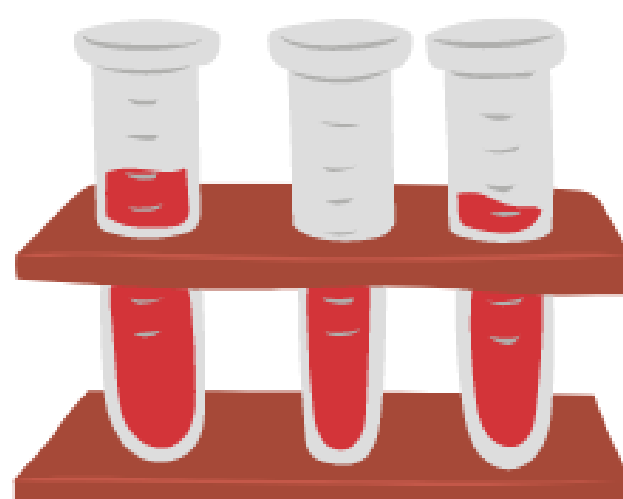
Additional medications, such as sulfonylureas, may be essential to manage the disease. Studies indicate that less than 60% of T2DM patients can maintain their blood glucose level at an optimal range, even with pharmacotherapies [9]. Using a combination of pharmacotherapies helps to increase the effect of medications. Nevertheless, there are problems with a combination therapy approach, especially with concerns for drug interactions, risk of side effects, and patient adherence [9, 10].

Miccoli et al. pointed out that patient adherence to prescribed oral diabetes medications affects their blood glucose level: higher adherence is correlated with lower hemoglobin A1C level (lower blood glucose level) [10]. Furthermore, side effects, which are more frequent when multiple medications are involved, is a major factor in causing decreased patient adherence [10]. The number of medications prescribed is also an important factor with patient adherence. Patients showed reduced adherence with metformin and sulfonylureas than with either monotherapy [10]. Thus, reducing the number of tablets required for treatment may improve patient adherence and treatment effectiveness [10].

Sulfonylurea is another commonly prescribed oral medicine for managing T2DM. It functions by increasing insulin secretion in beta-pancreatic cells to reduce hyperglycemia. Sulfonylurea inhibits the ATP-sensitive potassium channel in beta-cells, which causes their depolarization and thus the release of exocytosis vesicles containing insulin into the blood. Metformin has lower cardiovascular mortality than sulfonylurea; however, their ability to lower blood glucose levels, as measured by the amount of glycated hemoglobin in the blood (HbA1C), are similar [11]. Studies by Roumie et al. in T2DM individuals with kidney impairment have also demonstrated that metformin resulted in fewer major adverse cardiovascular events than sulfonylureas [12]. Furthermore, sulfonylurea also increases the risk of hypoglycemia compared to other medications [11].

Imeglimin is a prospective oral medicine for treating type 2 diabetes mellitus; it is currently in phase III clinical trial. Imeglimin decreases glucose synthesis in the liver and increases glucose uptake in muscle cells [9]. It increases insulin signalling in liver and skeletal muscle cells of mice, with an observed increase in PKB (Protein kinase B, Akt) phosphorylation downstream [13]. Phase II clinical trial comparing the effects of imeglimin and metformin on individuals with T2DM documented a few cases of adverse effects in groups treated with imeglimin, and fewer gastrointestinal side effects with imeglimin than with the metformin treatment groups. A slight increase in insulin secretion was observed after administration of imeglimin [9]. Lower glucose level was also evident with different doses (500mg, 1500mg) of imeglimin given twice daily in a 4-week clinical trial [9]. Thus, imeglimin may be a suitable alternative for metformin as it has slightly fewer side effects and works through similar mechanisms as metformin.

Diabetes, and especially type 2 diabetes, is an increasingly prevalent disease around the world. Due to its progressive nature, diabetes cannot be cured and must be controlled with treatments. Metformin and sulfonylureas are commonly used oral medications for T2DM. Metformin is preferred between the two due to its lower risk for cardiovascular or hypoglycemic side effects [11]. There are concerns with both oral medications, so better alternatives are always on demand. Potential anti-diabetics, such as imeglimin, maybe a suitable alternative to metformin and sulfonylurea.



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Prenatal Treatments for Cognitive Deficit in Down Syndrome

By: Hanna Zhu

Down Syndrome (DS) is a type of aneuploidy caused by an abnormal trisomy in chromosome 21. It is among the most prevailing and well-known neurodegenerative diseases, with an approximate occurrence of one in every 780 newborn babies in Canada. [1] On the molecular level, DS is predominantly caused by non-disjunction, an abnormal event during cell division. A smaller percentage is caused by translocating the extra 21st chromosome in the genome. The extra 200 to 300 genes on chromosome 22 are responsible for clinical features. Immediately after birth, the diseases can be diagnosed based on the baby's physical appearance. Small limbs, slanted eyes and flat heads are some typical features. Usually to confirm the disease, a chromosome karyotype is performed.

Symptoms may reveal once born or happen throughout one's life, so constant screening and surveillance are required. Following onset of the disease, a patient may experience a series of cardiac, pulmonary, auto-immune, and oncological complications, in which respiratory infection and heart failures [1] are two leading causes of premature death in DS patients. In later stages, both the cognitive function and health tend to worsen, coupling with social disconnection and incompletion. Therefore, the average life expectancy in people with DS rarely exceed 45 in the past before 1960s. [2]

With advancing treatment options and rising social awareness, the life quality of DS Patients has been dramatically improved in the past decades. Anticonvulsants are now applied to treat seizures, and surgeries are performed to correct cardia defects and airway obstructions. DS patients can now live a 'nearly' normal life. What about learning and speaking abilities? Can cognitive dysfunction also be corrected? Unfortunately, an effective prenatal treatment has not been found yet.

Postnatal treatments did alleviate symptoms, while the root problem persists. So, finding ways to treat the disease once detected during pregnancy becomes the common goal.

Curcumin's unique properties make it attractive to many researchers. It is a type of polyphenol phyto-constituents found in curry and food additives that have been intensely studied over the past decade. Anthocyanins from berries, resveratrol from peanuts and catechins from tea are all examples of polyphenols. This group of chemicals are powerful antioxidants with anti-inflammatory properties, with potential effects on multiple cellular signaling pathways. Among those, curcumin is the most widely studied [3].

The postnatal effects of curcumin had been discovered early since 2000. In 2007, Chinese scientists Xu and colleagues demonstrated that curcumin played a similar role to antidepressants which relieved neurogenesis stress in rats [6]. By 2011, evidence had showed that curcumin could reduce protein aggregation, activate microglial cells, and improve spatial memory [7]. But the prenatal clinical effects of curcumin hadn't been examined until recently.

In late July this year, Rueda and colleagues conducted a set of experiments using Ts65Dn (TS) mouse model, a widely adopted model that resembles the DS karyotype and phenotype [8]. 65 pregnant female TS mice were injected with curcumin at a neuro-protective dose. The offspring were then divided into four groups, control litter prenatally treated with curcumin (CO-C) or vehicle (CO-V), and TS litter treated with curcumin (TS-C) or vehicle (TS-V). The short-term effect was determined by removing the brain and freeze it for immunohistochemistry and staining.

Interestingly, the results indicated an immediate boost of brain weight and density in both the TS-C and CO-C groups compared to their vehicle mates following prenatal curcumin injection.

Given that most prenatal treatments involve interfering with brain development, safe and natural compounds were strongly preferred. Aside from curcumin, fatty acid was recognized as another potent candidate. Around the same period, the same model was used in Spain by García-Cerro and colleagues, where prenatal administration of Oleic Acid and Linolenic Acid was conducted [5]. Similarly, short-term effects through DAPI staining revealed that there's increased brain weight in TS mice injected with oleic acid at postnatal Day2 (PD2) compared to those treated with vehicle. Linolenic acid exerted similar effect to a lesser degree. Long-term effect of prenatal treatments was evaluated from PD45. They discovered that treating with oleic acid leads to an increase in postsynaptic density protein 95, an essential post synaptic marker number, in all areas of the hippocampus, where the effect of lineoid was partial. Moreover, TS-LNA and TS-OA mice display lower latency, greater working memory and more crossings in the given quadrants compared to TS-V and TS-V mice.

The prenatal treatments have brought light to people suffering from DS and other debilitating diseases, but there are problems regarding usage and dosage of the chemicals. Despite that polyphenol has the amazing ability to cross the blood-brain barrier, a critical property for a neurotherapeutic agent, its poor bioavailability in the neural tissue remains a major drawback. According to Mythri and Bharath, curcumin accumulated in the brain, but it remained active only for a short period, which had been confirmed by other researchers [9]. Therefore, there's still room for improvement considering the administration of curcumin to produce long-lasting effects. Possible future clinical interventions may include extensive trials on substances that can be co-administrated with curcumin to promote its life cycle, as well as the incorporation of various drug delivery system, like the use of nanoparticles for efficient delivery of drugs.



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The Treatment of Osteosarcoma with MAP and MAP-Related Regimens

By: Faizah Abdullah

Cancer is a widespread illness occurring from the loss of the standard cell proliferation that is essential for the development of an organism. It is often difficult to treat upon its metastasis to other locations within the body. The impact of cancer is widespread as it is a prevalent disease that affects the lives of many individuals around the globe. Osteosarcoma is a bone cancer which frequently arises in adolescents during puberty when there is additional bone growth[1]. Tumours are typically found in the femur, tibia, or humerus upon imaging, shown in Figure 1, after a patient develops stubborn pain in the affected area for a prolonged period of time[2]. Osteosarcoma can also metastasize to other locations within the body presenting further challenges in treatment[1]. Chemotherapy is essential to prevent disease recurrence prior to and following surgery to remove the primary tumour[1].



Figure 1: Osteosarcoma as shown on x-ray images. The tumour is emerging in the humerus on the right and in the tibia on the left.² Images obtained from Wittig et al[2].

An essential component of osteosarcoma treatment is surgery due to the location and nature of the cancer.

Since it commonly occurs in the extremities, it can often be treated with a limb salvage surgery in which the primary tumour is carefully removed and the function of the limb is preserved[2]. However, some tumours require amputation of the extremity[2]. Along with this surgical resection, chemotherapy is necessary to be administered in an neoadjuvant fashion – prior to the surgery – and and adjuvant fashion– following the surgery[1]. Delivering adjuvant chemotherapy after pri-mary tumour removal is essential to prevent regrowth of the tumour, as it was found that >80% of osteosarcoma patients who were not given chemotherapy following primary tumour removal relapsed[5]. In addition, neo-adjuvant chemotherapy administration prior to the surgery is also essential to promote tumour cell death and shrinkage, allowing for the removal of the tumour within larger margins to prevent tumour regrowth[2].

Several chemotherapies can be used in the treatment of osteosarcoma, including methotrexate, doxorubicin, cisplatin, ifosfamide, and etoposide[2-4]. The typical protocol for treatment includes methotrexate, doxorubicin, and cisplatin – called the MAP treatment[2,4] however, additional drugs can be added to this treatment with varying impacts[2-4].

The three main drugs that are part of the MAP regimen are methotrexate, doxorubicin, and cisplatin[2,4]. Doxorubicin is a drug which blocks additional cell growth by directly preventing the creation of new DNA and RNA through intercalation.² Cisplatin is similar to doxorubicin in also directly preventing the production of new DNA by denaturation[2].

Because the creation of new cells depends on the synthesis of DNA and other significant cellular components like proteins and organelles prior to mitosis, the obstruction of these steps will hinder cellular proliferation.

Methotrexate is different from doxorubicin and cisplatin in that it does not directly impede the creation of new cellular elements, but is an antimetabolite which stops the creation of purines[2]. Because purines are essential as nitrogenous bases for DNA replication, a drug which blocks their production would be detrimental to the cell cycle. All of these drugs participate in obstructing the processes that are essential for cellular growth and proliferation, working to block the basis of cancer

Toxicity is a great concern with chemotherapy drugs in the treatment of cancer, as it can cause unwanted complications in treatment and can also have harmful life-long effects.

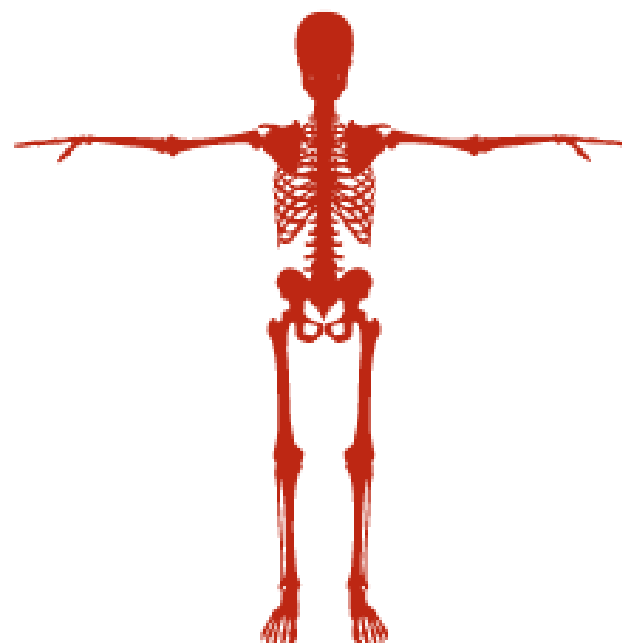
Chemotherapies often have many different side effects that can cause secondary issues, such as cardiomyopathy from doxorubicin[2], and ototoxicity from cisplatin[2].

However, a meta-analysis of several studies investigating the impact of the MAP protocol in osteosarcoma treatment found that it resulted in less toxicity, including a reduction in anemia and thrombocytopenia, than other combinations which included ifosfamide, etoposide, or additional chemotherapeutics[4]. Link et al.

notes that the side effects of an adjuvant MAP-related protocol including methotrexate, doxorubicin, cisplatin, and a combination of bleomycin, cyclophosphamide, and dactinomycin were primarily manageable, with only 16% of patients developing a deadly hematologic effect[5]. However, they also note that the toxicity of the chemotherapeutics resulted in two deaths in their study[5]. Although these drugs have the toxicity issues described above, they also contribute to a 66% 2-year survival rate without a relapse in osteosarcoma patients[5].

A meta-analysis of MAP and MAP-related protocols found that the 3-year survival rate was not dissimilar between patients who received the original MAP treatment or those who were given the MAP-related protocol with supplementary drugs[4]. Another study which investigated the administration of the MAP protocol against a MAP adjuvant regimen in patients which included ifosfamide and etoposide found that there was no difference in the survival rates between the two groups, with the two additional drugs instead only promoting a greater toxicity in patients in which neoadjuvant chemotherapy was not positively received[6]. However, in a separate study of different combinations delivered neoadjuvantly to patients suffering from osteosarcoma, a MAP-related protocol which included ifosfamide was found to have the greatest 5-year survival rate (72.5%) when compared to only MAP (67.5%) or a protocol with only the drugs methotrexate and doxorubicin (40.6%)[3].

The literature suggests that further research is necessary to establish the efficacy and benefits of supplementary treatment in addition to the MAP protocol. It is prudent to evaluate both the toxicity of the drugs and their efficacy in treating osteosarcoma, as drugs will be most beneficial when their toxicity is minimized and their efficacy is maximized. Ultimately, the use of MAP and MAP-related protocols in the treatment of osteosarcoma can present great benefits in promoting patient survival.



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Uncovering the Impact of COVID-19 on Mental Health and Treatments

By: Ersi Zabzuni

The social nature of humans has provided an evolutionary advantage and is deeply rooted in our genes. With the emergence of COVID-19 and enforcement of social isolation, this distinguishing feature is being heavily challenged. The pandemic has been associated with an increased prevalence of a plethora of mental health crises, such as depression, insomnia, stress and anxiety[1]. With an increase in mental health illnesses comes a need for adaptation of pharmaceuticals. This includes a greater investment in compounds to treat these illnesses, and the adjustment of existing ones. The world health organization reports significant disruption in critical mental health services in 93% of countries affected by COVID[2]. These services present in the form of counselling services, psychotherapy and importantly, pharmacotherapies. To put things into perspective, buprenorphine is not as widely available for the individual that used to struggle with a heroin addiction (45% reduction) and doxepin is not as widely accessible for the individual that has finally found an efficacious antidepressant for their symptoms (30% reduction)[3]. The pandemic has been predicted to contribute to an additional 75,000 deaths globally linked to suicide and substance abuse as a result of increasing mental health crises and reduced emphasis of interventions.

What are some alterations in medication use?

The COVID-19 pandemic has transformed accessibility to mental health drugs and also altered the way they are being administered. Authorities in several countries have urged individuals to reduce visitation to hospitals to avoid possible exposure to the virus. This has led to the emergence of online consultations by psychiatrists and other specialists. Unfortunately, some aspects of health cannot be captured using this method. The pandemic has also

changed the way some medications are administered. For example, long-acting injectable (LAIs) antipsychotics are no longer preferred and have been replaced with oral antipsychotics[4]. As injectable drugs reach high plasma concentrations extremely quickly and have a rapid onset of action, their use must be supervised, especially in a vulnerable population. A study from Romania found a 90% decrease in injectable olanzapine and a 81% decrease in injectable paliperidone prescribed[4]. On the other hand, antipsychotic use in patients with dementia has substantially increased. Due to COVID-19 restrictions, many individuals in long-term care homes no longer have visits from their family and cannot participate in activities, resulting in a surge of psychosis and other psychotic symptoms. This is worrisome as the safety and efficacy of antipsychotics in patients with dementia has been questioned and brings up many ethical considerations. Clozapine, another antipsychotic, has been associated with an elevated risk of contracting COVID-19 according to a study from the United Kingdom[5]. Clozapine is an important antipsychotic because it is effective in treatment-resistant schizophrenia and has resulted in a reduction of suicide rates amongst this population. However, with double the chance of developing pneumonia on the line, it may no longer be considered for some patients[5]. Adjustments to the regimen of antipsychotic use in specific may need to be made as a result of limitations COVID-19 poses.

What are the implications on COVID patients?

Individuals infected with COVID-19 can be given a variety of pharmaceuticals as treatment, such as Remdesivir or Chloroquine. A possible side effect of these drugs is depression, anxiety and fear, which introduces the question: can psychotropic medications be used in conjunction with antivirals?

The short answer is some combinations are safe and effective, while others may be detrimental. For example, atazanavir inhibits CYP3A4, resulting in higher serum pimozone levels when taken together. This could cause lethal effects, such as torsades de pointes and heart failure[6]. Similarly, atazanavir causes increased serum levels of anxiolytic midazolam when taken together, causing prolonged sedation and increased time spent in hospital[6]. A common side effect for almost all drugs used to treat COVID-19 is QTc prolongation, which is a delay in ventricular repolarization and can be fatal if it induces arrhythmias. Coincidentally, some psychotropics are also known to have the same effect, meaning a combination of these two types of drugs can be lethal[7]. It is also important to mention that patients infected with COVID are vulnerable to developing various mental health issues such as depression and anxiety[8]. Drugs used to treat COVID patients may also result in the same effects, further adding to the discouraging mindset already induced[8]. Drug-drug interactions become particularly important in this case and it is important for health-care providers to pay attention to them when treating COVID patients.

What does this mean for the future?

With the pharmaceutical industry focusing on COVID treatments and vaccines, attention is taken away from other important initiatives, such as psychiatry. In the immediate future, a phenomenon called “panic buying” is expected to increase. Panic buying refers to an induced demand for accumulating medication and is more prevalent in chronic disorders, such as anxiety and depression. Excess buying for mental medication has already gone up by 0.4% in the USA and is expected to surge[9,10]. This further depletion in supply can take away from other individuals that require the same medication and should be limited. As COVID-19 is overshadowing mental health illnesses, it may be important to shed some light on how detrimental they are for some individuals. Allocating a higher budget to psychotropics may be of interest to prepare for the secondary effects of COVID.

It is also important to strategically select specific mental illnesses to research treatments for. For example, alcohol consumption has increased in about 25% of Canadians aged 35-54 ever since the pandemic began[11]. Other individuals may cope using more potent drugs, such as opioids. Therefore, it may be important to invest in greater production of naloxone to prevent opioid overdose or efficacious treatments for excessive alcohol use, which have not yet been discovered. COVID is expected to cause up to 2114 excess deaths in 2021[11], therefore making psychotropics and other assistance available to everyone in need is crucial.

Closing remarks

Stress, grief, unemployment, and uncertainty all play into a positive feedback loop caused by COVID-19 and result in a rise of mental health illnesses. The use of pharmaceuticals has been altered due to less in-person monitoring available and risks present when administered simultaneously with COVID treatments. Therefore, it may be important to assemble new treatment regimens or produce a system that is able to manage this predicted overload in patients. Although it is easy to fall into a negative, fixed mindset during these tough times, some initiatives have been made to alleviate mental health concerns[10,11].



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Delving into the History of Breast Cancer Pharmacotherapy

By: Anupama Bhadwal

Over 25% of cancer cases diagnosed in Canadian women are of breast cancer, making it the most common form of cancer diagnosis in this population. Approximately 1 in 8 Canadian women will develop breast cancer, with it being fatal in approximately 1 in 33 cases. Breast cancer also occurs in men but is rare, with an estimated 240 cases compared to the estimated 27,400 in 2020 that occurred in Canadian women[1].

Breast cancer often occurs due to mutations in either or both of the DNA and RNA present within breast cells. Cells in the lobules supplying the milk ducts or the inner lining of the ducts themselves are the most commonly affected[2]. The most common mutations observed are those in the breast cancer gene 1 and 2 (BRCA1 and 2) and the human epidermal growth factor 2 (HER2). These are oncogenes and mutations or extra copies of these genes may lead to uncontrolled cell proliferation. BRCA1 and 2 mutations have the potential of increasing the risk of a woman developing breast cancer in her lifetime to almost 85%. Reproductive history, use of oral contraceptives, ionizing radiation exposure are also factors contributing to breast cancer development risk[3].

To gain a better appreciation and understanding of breast cancer therapy, one must delve into its history. One of the early pioneers in the field was Dr. William Stewart Halsted, surgeon and professor at John Hopkins. He prioritized skill and technique in a field which was used to employing brute force, and started the practice of wearing gloves during surgery[4]. In the late 1800's, Halsted performed the first radical breast mastectomy, which became the standard treatment for breast cancer for years to come. The procedure involved mammary gland, pectoral muscle, and axillary lymphatic tissue excision[5]. The radical approach, which left patients disfigured and with problems like hyper edema, was considered crucial

to remove all of the tumor[6].

Radiation therapy was the next revolution in the field of breast cancer treatment. In 1895, Wilhelm Röntgen discovered X-rays that could carry radiant energy through human tissue and deposit some in it. With this in mind, in 1896, Dr. Emil Grubbe used a vacuum X-ray tube to bombard the breast tumor of a patient, and thus discovered the potential of radiation to treat local cancers[7]. Marie and Pierre Curie's 1898 paper on the discovery of radium had a synergistic effect on cancer therapy progress. This element allowed medical professionals to use energy bursts, that were a thousand times more powerful, on the target tumor[8].

Early screening was the next area propelling progress in this field. In 1913, a German surgeon, Albert Salomon, analyzed 3000 mastectomies, using X-rays. He discovered microcalcifications in the tissue which gave an overview of the form and spread of the tumors. In 1949, Raul Leborgne introduced the breast compression technique for breast imaging, and in the late 1950s, Robert Egan used fine-grain intensifying screens leading to clearer imaging. Thus, mammography came into being and in 1969 was introduced for early tumor detection[7]. The next big development was the introduction of chemotherapy. In 1963, oncologist Paul Carbone at the National Cancer Institute (NCI) launched a trial to investigate the effectiveness of chemotherapy following early stage breast tumor removal. Results showed that surgery followed by chemotherapy decreased the relapse rate. Following these findings Italian oncologists Gianni Bonadonna and Umberto Veronesi conducted a large-scale randomized trial to investigate adjuvant chemotherapy following early stage breast cancer surgery. A tolerable concoction of Cytosin (alkylating agent), methotrexate (antifolate), and fluorouracil (DNA synthesis inhibitor), known as CMF, was used.

The 10, 20 and 30 year follow-ups clearly supported adjuvant chemotherapy for breast cancer patients,[9] which encouraged future research into new possible concoctions and regimens.

As time wore on, upcoming surgeons, including Dr. Bernard Fisher from Philadelphia, began to question the merit of a radical mastectomy. In 1971, four years after becoming the chair of the National Surgical Adjuvant Breast and Bowel Project (NSABP), Dr. Fisher launched a systematic, randomized trial on the effectiveness of a radical mastectomy[10]. There were three groups: one receiving the radical mastectomy, the second receiving a simple mastectomy and the third receiving surgery followed by radiation therapy. When results were made public in 1981, it was revealed that there was no difference in the rates of recurrence, relapse, distant metastasis and death. This provided more insight into the concept of metastasis, and explained why many patients still succumbed to the disease after a radical mastectomy. The bold procedure which had left numerous disfigured is now rarely practiced[7].

In 1962, a patent was filed by the Imperial Chemical Industries (now AstraZeneca) for Tamoxifen as a contraceptive, but the drug was found to have the opposite effect and led to an increase in fertility. In 1896, Dr. George Beatson discovered estrogen as a factor influencing the growth and development of breast cancer. Arthur Walpole, the leader of the Tamoxifen development team, saw the potential to treat estrogen sensitive breast cancers with this drug and teamed up with oncologist Mary Cole to launch a trial in 1969. Tamoxifen, an estrogen receptor antagonist in breast tissue, showed immediate tumor volume decline in patients with estrogen receptor positive tumors and had reduced side effects as compared to other therapies at the time[11]. In subsequent years, Fisher determined that Tamoxifen was effective in reducing the incidence of invasive breast cancer in high risk patients by 50%. It also acted as an effective adjuvant to breast cancer surgery for estrogen receptor positive tumors that had not spread past the axillary nodes[12].

The drug, however, had unforeseen side effects: Tamoxifen is a first generation selective estrogen receptor modulator (SERM) and has a mixed pharmacology, due to the expression of different estrogen receptors in different tissues. Therefore, it is also an estrogen receptor agonist at tissues like the uterus, heightening the risk of developing endometrial cancer[13]. The development of second and third generation SERMs hope to mitigate these issues.

Monoclonal antibodies (mAbs) have also emerged as a pharmacotherapy in the field. Cases of breast cancer with a HER2 mutation are known as HER2-positive breast cancers due to the overexpression of HER2 protein on the cell surface. Trastuzumab, a mAb is administered intravenously to HER2 positive patients. Combined with chemotherapy, patients show better responses than those who only receive chemotherapy. As a mAb, it attracts immune cells to the tumor via antibody-dependent cellular cytotoxicity. Additionally, it is hypothesized to induce internalization and degradation of HER2[14].

Breast cancer pharmacotherapy has come a long way in improving the prognosis for millions. From Halsted's radical mastectomy, Fisher's trials, the implementation of chemotherapy, radiation therapy, SERMs and mAb therapy, the field has progressed in ways unforeseeable a century ago. This journey highlights the innumerable efforts, collaborations, and contributions that were made worldwide by professionals all united to fight a common cause. However, this is not the end of the journey in our fight against breast cancer, and the hard work of many scientists and doctors is yet to come to the forefront and change the scientific understanding of the disease as we know it.



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Big Pharma's Influence on the Media and Public

By: Daniella Ekmekjian

Big Pharma has successfully maintained a monopoly and immense influence over the healthcare sector, further legitimizing their capacity to coercively utilize the media in a manner that works to manipulate public narratives, attitudes and perceptions. Pharmaceutical companies primarily advertise their drugs and pharmaceutical products through Direct to Consumer Advertising (DTCA), which refers to the practice of marketing merchandise through various media platforms ranging from academic mediums to television news and social media (e.g. Facebook, Twitter)[1]. Through this, pharmaceutical companies are enabled to downplay the associated risks and oversell certain benefits of a drug by generating false positive images within advertisements in order to achieve their goal of maximizing profits. Rates of over-prescription, misprescription and the unnecessary medicalization of patients are markedly increasing, giving rise to irreversible health consequences.

False positive imagery deliberately mobilizes vulnerable members of society by compellingly advancing the notion that certain drugs are required to increase their quality of life[1]. This drastic shift in attitudes following the viewing of pharmaceutical advertisements directly corresponded to the images portrayed within the commercial, namely those of happy couples partaking in activities they could not prior to taking the drug and families gathering for a celebration on a sunny day following the ill member taking the drug[2]. Consumers are unconsciously led to hyper-focus on the benefits and the idyllic nature of the life promised by the drug rather than long lists of side effects which are often read at such a fast pace that they are incomprehensible. This overt disconnect between the verbal narration and false positive imagery promotes the "insufficient processing of verbally presented risk information," diminishing harmful con-

sequences under the guise of a happy life and perfect health[2(p674)].

Through the overuse of false positive imagery, pharmaceutical companies are able to omit any information that does not conform to the attainment of their economic interests of generating profit[3]. In doing so, "84% of regulatory letters regarding direct-to-consumer advertising cited advertisements for either minimizing risks [...], exaggerating effectiveness [...], or both." [4(p677)]. Pharmaceutical companies are thereby exceedingly cautious with the language and syntax used within their advertisements, which commonly present particular risks in a vague and ambiguous style to consumers[4,5]. Presenting adverse effects in such a way effectively bars consumers from engaging in autonomous decision-making processes, specifically regarding courses of treatment to produce the greatest benefits.

The aforementioned actions coalesce to over-medicalize trivial health conditions by causing over-prescription and misprescription of medications for menial conditions. The maintenance of public health is thus sacrificed for profits and economic gain. In combination with DTCA, consumers are often left with a biased preference towards a drug and in certain instances, will request a drug even in cases where it is ineffective for their condition[3]. Surprisingly, it was also reported that even after a physician informed their patients that a specific drug may cause long-term harmful effects, some patients persisted in obtaining the drug[3]. A study conducted by Robinson et al. (2004) revealed a moral dilemma that arises in the physician-patient relationship, wherein physicians often prescribed advertised drugs as they felt pressured to protect and maintain relationships with their patients[5]. In these ways, Big Pharma's ultimate goal of maximizing profits is achieved through the over-prescription and misprescription of drugs advertised through DTCA.

In conclusion, Big Pharma is able to manipulate and control what drugs are advertised and how they are perceived by society. This grants pharmaceutical companies with the power to skew public perceptions of certain drugs, causing individuals to normalize the use of drugs as a means to achieve a fulfilled life. Primarily achieved through the use of false positive imagery and DTCA, pharmaceutical companies paint a moral veneer over the adverse effects their drugs can cause by overselling the benefits. As a result, the over-medicalization of patients and consumers occurs due to the overprescription and misprescription of pharmaceutical products, ultimately fostering a flawed view of health and the healthcare system.



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Antibiotic Resistance: The Mechanistic Basis and Interactive Areas

By: Parnian Baharlouei

The discovery of antibiotics has been associated with the development of bacterial resistance, just as it has helped treat bacterial infections. The mechanism for the generation of bacterial resistance varies, including the intrinsic resistance of organisms, the development of resistance due to spontaneous genetic mutations, and the acquisition of resistance genes by bacteria. To control antibiotic resistance, the interaction between the four factors must be considered: the patient, the drug used, the organism, and the environment. It should be borne in mind that the relationship between these factors determines the status of antibiotic resistance.

Introduction

The treatment of bacterial infections in the twentieth century with antibiotics has been one of the most prominent human achievements. The first attempt was made by Fleming to extract penicillin from the fungi that produced this antibiotic. Then the effort to extract anti-bacterial material from other micro-organisms continued, leading to the production of β -lactam antibiotics, which include penicillin and cephalosporins, tetracyclines, and aminoglycosides, such as streptomycin and vancomycin. Attempts to produce synthetic antibiotics have also led to the development of Sulfa drugs and fluoroquinolones[1]. The beginning of attention to the problems and concerns related to antibiotic resistance dates back to the time of World War II when resistance to Sulfa drugs emerged and then *Streptococcus Aureus* (SA) was recognized as a model bacterium for resistance to penicillin soon after Fleming discovered penicillin[2]. After developing resistance to penicillin through the production of β -lactamase in bacteria, methicillin was introduced, which is a derivative of penicillin and is resistant to bacterial β -lactamase. Soon after the introduction of methicillin, however, Methicillin-resistant *Streptococcus*

aureus (MRSA) emerged[3]. Bacterial resistance evolved over time, and in the late 1950s and early 1960s multidrug resistance was observed in *Escherichia coli*, *Shigella*, and *Salmonella* bacteria, which are among the enteric bacteria[4]. The discovery that the bacteria were able to transmit antibiotic resistance through plasmids raised concerns in 1963-1981. The emergence of antibiotic resistance has become a shared global problem in the present era, with increasing concerns and attention to this problem[2].

Antibiotic resistance mechanisms of action

Mechanisms of resistance in bacterial species can be divided into three categories: intrinsic resistance, resistance caused by spontaneous genetic mutations, and acquired resistance caused by receiving a gene cassette in various ways, known as Horizontal Gene Transfer (HGT). Intrinsic resistance itself is divided into two categories: first, the prevention of bacteria from antibiotics entering through the cell wall; and second, the production of efflux pumps or other internal substances that hydrolyze and deactivate the antibiotic. Intrinsic resistance can be generated by the production of (β)-lactamase enzymes by Enterobacteriaceae to destroy the β -lactam ring in β -lactam antibiotics[5]. Efflux transmembrane pumps, especially in *Pseudomonas*, pump antibiotics out of the cell to keep the antibiotic concentration in the bacterial cells low[1]. Other ways of intrinsic resistance in bacteria are to chemically alter antibiotics through the production of various enzymes. Chemical changes such as acetylation, phosphorylation, and adenylation of antibiotic molecules can cause steric hindrance of these molecules and ultimately reduce their effectiveness. Modifying enzymes include aminoglycoside modifying enzymes (AMEs) that alter the hydroxyl group or the amino group of aminoglycoside anti-biotics[6].

Another way to build bacterial resistance is through genetic mutations. For example, a base substitution mutation in the 23s rRNA gene or a mutation in the L22 and L4 ribosome proteins can cause bacterial resistance to macrolide antibiotics. In addition, resistance to quinolone, sulfonamides, and trimethoprim can be induced by SNPs, and streptomycin resistance can be induced by mutations in the ribosomal S12 protein (rpsL gene)[7]. Acquisition of a gene cassette by bacteria can occur in a variety of ways, such as from other bacteria, phages, or free DNA in environments in the form of plasmids and transposons. Among the bacterial species that produce this resistance is MRSA. In various SA species, the *mecA* gene, which encodes a protein responsible for cell wall production and is insensitive to β -lactam antibiotics, has been shown as the horizontal transfer of this gene between SA species. Other mechanisms of bacterial resistance include changes in the bacterial target to prevent antibiotic binding, elimination of drug entry through the cell membrane using down-regulation of these sites (this mechanism is especially seen in gram-negative bacteria), and finally, bypassing the antibiotics' mechanism of action through cellular pathways[5,8,6]. One mechanism that occurs by reducing the susceptibility of the antibiotic target is observed in vancomycin-resistant enterococci (VRE), which is seen by reprogramming the target in bacteria[1]

Interactive areas for antibiotic resistance

For the development of antibiotic resistance, the interaction between four factors must be considered: the patient, the drug, the microorganism, and the environment. In patients, many factors are involved in the development of bacterial resistance. For example, the presence of an inoculum infection increases the likelihood of pre-existing resistant mutant species. Also, the presence of a foreign body or compromised immune system can slow the clearance of infection, which can lead to the selection and growth of

resistant species in the site. Antibiotic treatment can also come into contact with the normal flora of the body and lead to the development of resistance in them, and eventually, this resistance is transmitted to pathogenic organisms[9,6]. Drug-related factors also play an important role in resistance. Narrow-spectrum drugs have less influence on the normal flora of the body and are therefore more beneficial than broad-spectrum drugs. Dosage and antibiotic combination are also effective factors in developing antibiotic resistance. The use of high-dose antibiotics is beneficial because it increases the concentration of the drug in the place and as a result, less resistance is created[9,10]. Moreover, the combined use of antibiotics has been shown to be effective in preventing the creation and spread of resistance[9]. Another determining factor in the development of resistance is the type of organism and whether organisms that were resistant to antibiotics can become sensitive to the drug following the sudden removal of antibiotic pressure. Another concept is the ability of microorganisms to compensate genetically, and whether the resistance gene can remain in the genome for successive generations[9,11]. From an environmental perspective, various locations are considered, including hospitals, nursing homes, and communities, and whether these locations generate *de novo* resistance or contribute to the spread of resistance. Besides, evaluation of the drug's threshold usage that causes resistance plays an important role in the development of antibiotic resistance[11,9].

Closing Remarks

In this article, different mechanisms of antibiotic resistance are briefly mentioned. The four important and determining factors in the development of antibiotic resistance were also discussed. Each of these factors, including the patient, the drug, the organism, and the environment, play a key role, and a dynamic relationship between them must be considered to control antibiotic resistance.

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