Multiple Sclerosis: the viral link and antibody-based therapies

Multiple sclerosis (MS) is an autoimmune disease characterized by demyelination; lymphocytes and macrophages are drawn to the fibers of the white matter and start attacking the myelin sheath and killing the oligodendrocytes. This inflammatory response leads to either partial or complete demyelination, resulting in formation of scars and lesions. MS affects women more than men. Although the exact cause remains unclear, genetic factors as well as environmental triggers may be involved. Viruses such as Epstein-Barr Virus (EBV) and human herpes virus-6 (HHV-6) are strongly associated with the pathogenicity of this disease in genetically predisposed individuals. Symptoms depend on the affected area of the CNS with optic neuritis and motor disturbance as early symptoms. Despite the fact that there is no cure, disease modifying drugs are used to reduce relapses, progression rate, and number of brain lesions. These include β interferons, glatiramer acetate and mitoxantrone. In addition, there are also a number of monoclonal antibodies such as alemtuzumab, daclizumab and rituximab; with the only FDA approved one being natalizumab. Other antibodies still under investigation are ocrelizumab, ofatumumab and AIN457.

Diagnosis and disease course

To reveal the demyelination, cerebrospinal fluid (CSF) test should show increased levels of IgG. MRI is also performed to reveal any lesions during the diagnosis (1). As the disease progresses, axons are also destroyed due to death of oligodendrocytes which are responsible for nourishing the axons with insulin like growth factor and brain derived neutrophic factor. This process is termed Wallerian degeneration.

MS is divided into four types (1,2) depending on its severity and disease progression. The first and most common is relapsing remitting MS (RRMS) which appears to be experienced by all patients. This type has acute onset and is characterized by recovery periods following relapses which may last for days, weeks or even months, while remission can last from days to months.

As RRMS progresses, it becomes secondary progressive (SPMS) (second type). Only partial recovery occurs after relapses in patients with SPMS. Moreover, SPMS worsens on a slow steady state.

The third type is called primary progressive MS (PPMS) and is characterized by a slowly progressive course without any period of remission.

The last type is progressive relapsing (PRMS) which is rare. Disease progression rate is higher in adults. However, children experience a higher rate of relapse.

Viral links and causes

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That monozygotic twins show only 30% concordance in the incidence of this disease (3-5) supports the theory of environmental triggers such as viruses. Furthermore, CSF tests show increased levels of IgG and oligodendrocytes. These markers are seen in infectious diseases such as neurosyphilis and cryptococcal meningitis.

Additionally, a number of demyelinating diseases are caused by viruses (6). A study on mice also concluded that MS can be induced by a virus. In addition, upper respiratory tract infections are linked to increase in the rate of exacerbations episodes as well as their severity (3).

In the last decade a number of viruses such as measles, rubella, and herpes (3,7,5) have been implicated. EBV can induce trigger MS as evidenced by increased levels of antibodies specific to this virus, EBV DNA in serum, and anti-EBV killer T-cells (9). Human herpes virus-6 (HHV-6) has also been detected in patients’ brain (6).

**EBV**

This virus can hide in the immune system to trigger an inflammatory response that is responsible for demyelination (10). Patients who are affected by EBV have a higher rate of developing MS either immediately or after a period of virus exposure (8,9). Furthermore, people who are exposed to EBV are twice as likely as healthy individuals to develop MS (8). Moreover, there is an association between disease progression and anti-EBV antibodies (3). This virus may induce or trigger MS by the following mechanisms:

1. **Reactivation of the virus**
   
   Activation of the virus may also trigger immunological damage of the oligodendrocytes, which in turn may cause demyelination. Moreover, during exacerbations, a rise in anti-EBV early antigen was observed, which means reactivation of the virus leading to recruitment of T-cells. (6)

2. **Epitopic mimicry**
   
   Anti-EBV killer T-cells are misguided to killing both the virus and destroying an epitope of a protein component in the myelin sheath, (MBP) (7). The reason behind this is that the virus’s protein resembles one of the myelin sheath components. This epitopic mimicry explains the autoimmunity of the disease (8). However, MS may not be induced by this mechanism alone; it needs to be followed by non-specific immune response to initiate the disease.

**HHV-6**

HHV-6 DNA was detected in MS plaques in the brain (6). Infections caused by this virus may result in neurological complications and epilepsy. However, HHV-6 remains controversial as cause or trigger for MS as studies have failed to show the ability of this virus to activate MBP-reactive T-cells (11). Its mechanism in causing MS is thought to be by either molecular mimicry as EBV, direct cytopathic action or virus reactivation.

**Treatment**

MS therapy is composed of three categories: exacerbations therapy including steroids and plasmapheresis; symptomatic therapy including baclofen for muscle spasm, sildenafil for sexual dysfunction, and
amitriptylin for depression; and disease modifying therapy. Disease modifying drugs (DMDs) are classified into immunomodulators, immunosuppressants and monoclonal antibodies.

A. Immunomodulators

Immunomodulators are considered first line therapy. They include beta interferons (beta IFN-1a and 1b) and glatiramer acetate, which is composed of aminoacid polymers (12). They reduce the number of lesions when MRI is performed, and are used for RRMS (13). Both agents are used for clinically isolated syndrome (13-15).

Clinically isolated syndrome means the first attack, which is not yet a definite MS and is confirmed only when the second attack occurs. B IFNs are thought to act by decreasing the interaction between immune cells with other foreign cells, thus decreasing the inflammation which leads to demyelination (16).

Liver dysfunction and thrombocytopenia are contraindications for these drugs. Side effects include reaction at the site of injection and liver damage. Unlike glatiramer acetate, IFNs may show flu-like symptoms (14). To overcome this side effect, acetaminophen or ibuprofen should be taken prior to the interferon (13).

Each one of these agents has a different frequency of administration. Glatiramer acetate is injected daily via subcutaneous injection while beta IFNs are administered subcutaneously, either three times per week or every other day. Another beta IFN preparation can be given intramuscularly weekly (16).

The main drawbacks for using immunomodulators are their variable effectiveness and cost. Furthermore, the risks of prolonged usage are not known yet (13, 14).

The following three drugs are oral immunomodulators used in MS:

Fingolimod

Fingolimod slows the progression and reduces the number of relapses (17). It works by modifying a sphingosine 1-phosphate receptor leading to entrapments of T-cells and B-cells in the lymph nodes (17). It is an oral drug taken once daily. It is also indicated for RRMS when treatment with glatiramer acetate or interferons is ineffective (18). This medication costs more than other therapies and requires monitoring of heart function after the first dose for 6 h, because of bradycardia risk (17,19).

Teriflunomide

Teriflunomide is another oral immunomodulator used for RRMS (20, 21). It is the second oral medication approved by FDA after fingolimod because of its cardiovascular risks. Although beta IFNs and glatiramer acetate are used for clinical isolated syndrome, teriflunomide is the first drug that shows delaying in the progression to the clinically definite MS. This drug is used to reduce number of relapses and to slow the progression of MS. It reversibly inhibits dihydrorotate dehydrogenase, which has a role in DNA replication, thus, reducing T- and B-cell proliferation. Liver toxicity and teratogenicity are the major side effects. To avoid hepatotoxicity, patients should undergo monthly liver function tests for the first six months (21,22).

Dimethyl fumarate

Dimethyl fumarate is the third oral drug approved by FDA to treat MS. It is taken twice daily. It is used for patients with RRMS. It works by decreasing the number of immune cells, particularly lymphocytes. Infection, as a result of its mechanism of action, GIT disturbance and flushing are the most common adverse events (23).

B. Immunosuppressants:

Mitoxantrone is an FDA approved immunosuppressant for MS (16). This antineoplastic drug acts on T-cells and B-cells by destruction of their DNA and RNA leading to suppression of immune system activity (15, 24). It is used for RRMS, PRMS and SPMS but not for PPMS. Serious side effects, mainly cardiotoxicity confine this medication to only the severe stage of MS based on MRI results. Assessing baseline left ventricular function before starting this medication is essential (15). Mitoxantrone may also cause secondary acute myelogenous leukemia (AML) (12,15) and infection. Bone marrow suppression, thrombocytopenia and allergy are contraindications.

C. Monoclonal antibodies:

Monoclonal antibodies are becoming increasing popular in treating MS. To overcome immunogenicity, humanized or chimeric monoclonal antibodies are utilised. This process is carried out by attaching a small portion of a mouse monoclonal antibody, which is needed to recognize the targeted antigen, to a human antibody backbone. Super-humanized monoclonal antibodies are similar to chimeric monoclonal antibodies, but with attachment of a smaller
Alemtuzumab is another super-humanised monoclonal antibody that is used to treat leukemia (28, 33). It is used nowadays for patients with RRMS when first line therapy has failed (34). Reduction in the relapsing rate to 50% compared to beta IFNs and decreasing the progression of the disease have been observed (28,33). Moreover, the number of new lesions of patients with secondary progressive MS using this medication is reduced (33).

The mechanism of action of this drug is by binding to CD52, and killing T-cells in order to prevent them from entering into the CNS and initiate damage to the myelin sheath. This drug is given for five days intravenously and then after one year for three days. Common side effects are infusion reactions which can be prevented by pre-treatment with steroids or antihistamines, hyperthyroidism e.g. Graves’ disease, and idiopathic thrombocytopenia purpura (ITP) (35).

Daclizumab
Daclizumab is used to treat RRMS and SPMS in patients who failed to respond to beta IFNs or glatiramer acetate (36,37). It decreases the rate of progression and number of relapses. Additionally, it reduces the number of new lesions as indicated by MRI. Daclizumab is injected via monthly subcutaneous injections. This medication acts by binding to the tace-epitop on the interleukin-2 receptor (IL-2) against the CD25 receptor on the surface of T-cells. Daclizumab is designed to inhibit further inflammation, leading to protection of the myelin sheath against T-cells. Daclizumab also activates the natural T-cell killers (37-39). Some side effects such as fatigue and GIT disturbance may occur. Monotherapy shows similar efficacy to combination therapy with beta IFNs.

Rituximab
A chimeric monoclonal antibody used to treat non-Hodgkins lymphoma, rituximab targets CD20 antigen on B-cells. It decreases the number of B as well as T-cells in the cerebrospinal fluid and reduces the number of new lesions as well as relapses in patients with RRMS but is not effective for patients with PPMS. Improvement is seen after the first dose as indicated by MRI. It is only administered intravenously. Common side effects include progressive multifocal leukoencephalopathy (PML). This fatal complication is caused by JC virus, prior immunosuppressant treatment, and duration of natalizumab exposure. If a patient is on steroids or other immunomodulators they should stop taking them for at least one month before starting natalizumab monotherapy. To reduce natalizumab induced PML risk, patients should go through a drug holiday of 3-4 months after a year of taking natalizumab, but this comes with a risk of MS rebound. Longer half-lives and slower clearance are achieved with higher doses. Natalizumab is used for RRMS and not for patients with progressive form of MS. However, recent studies showed an improvement in patients with SPMS. (32)

**Natalizumab**
This is prescribed for patients who have had at least two severe attacks in one year with significant rise in the number of lesions on MRI (29, 30) and for patients who suffer from relapses despite the use of IFNs or glatiramer acetate (29, 31). It reduces the number of relapses by around 60-70%, as well as lesions and rate of disease progression (29,31,32).

Natalizumab is given as 300 mg intravenously every 28 days (30). This drug works by binding to alpha-4 integrins on the surface of lymphocytes, thus preventing immune cells from passing into the CNS (29). It is approved as monotherapy.

Common side effects include dizziness, infections and skin rash. One of the most serious infections is progressive multifocal leukoencephalopathy (PML). This fatal complication is caused by JC virus (29,31).

Several risk factors include previous exposure to JC virus, prior immunosuppressant treatment, and duration of natalizumab exposure. If a patient is on steroids or other immunomodulators they should stop taking them for at least one month before starting natalizumab monotherapy. To reduce natalizumab induced PML risk, patients should go through a drug holiday of 3-4 months after a year of taking natalizumab, but this comes with a risk of MS rebound. Longer half-lives and slower clearance are achieved with higher doses. Natalizumab is used for RRMS and not for patients with progressive form of MS. However, recent studies showed an improvement in patients with SPMS. (32)

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**Alemtuzumab**
Alemtuzumab is another super-humanised monoclonal antibody to a whole human antibody framework.

Variation of dosage forms can also help in reducing immunogenicity. For example, the intravenous form produces less immune reaction than the subcutaneous one. However, infusion reaction is another problem. (25, 26) Treatment with monoclonal antibodies should only be considered for patients who have severe progression despite the use of first line therapy immunomodulators (27).

Antibodies used in MS include natalizumab, alemtuzumab, daclizumab and rituximab. Only natalizumab is FDA approved and licensed while alemtuzumab and daclizumab are in phase III and rituximab still in phase II. (28)

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**Pregnancy and MS treatment**

Pregnant women experience reduced number of relapses, and stabilization of the disease. This is explained by the increased production of corticosteroids and some natural immunosuppressants during pregnancy. However, rate of relapses may increase significantly in the first three months after delivery when compared to its rate before gestation. Long term disability progression is not affected by pregnancy. Glatiramer acetate, β IFNs, fingolimod, teriflunomide, mitoxantrone, natalizumab, and rituximab should be discontinued during pregnancy. Intravenous steroids can be used in case of relapse. (42)

**Monoclonal antibodies vs DMDs**

DMDs include immunomodulators such as beta IFNs and glatiramer acetate, immunosuppressants like mitoxantrone and the new oral DMDs fingolimod, teriflunomide and dimethyl fumarate. DMDs reduce relapse rate and progression of the disease, as well as number of new lesions. Compared to monoclonal antibodies, they may differ in terms of efficacy, indication, route of administration and safety profile.

**Efficacy**

In terms of efficacy, natalizumab is more effective than β IFNs in slowing the progression of disease and reducing the relapsing rate (31). In addition, it can be used in the progressive form of MS (32). When alemtuzumab was compared to β IFNs, alemtuzumab was associated with greater reduction in rate of disability and decreased number of relapses (28,33).

**Indication**

β interferons and glatiramer acetate are considered first line therapy for patients with RRMS as well as patients with clinically isolated syndrome (13-15). Although mitoxantrone is used in progressive form of MS, it comes with serious side effects like cardiotoxicity and acute myelogenous leukemia. Natalizumab, alemtuzumab, and daclizumab can be taken in case of a more progressive form of MS like SPMS (32,33,36,37).

**Routes of administration**

All monoclonal antibodies, glatiramer acetate, and β IFNs are taken via injections; either subcutaneously like daclizumab or via infusion like natalizumab, alemtuzumab and rituximab. In contrast, there are three oral medications, such as fingolimod, teriflunomide, and dimethyl fumarate, which may be preferable to patients.

**Safety**

There is a risk of PML with natalizumab. It should be prescribed only for patients who test negative for JC-virus before initiating therapy (43). Alemtuzumab is associated with rare side effects like thyroid disorders and idiopathic thrombocytopenia purpura (28,33,35). In contrast, β IFNs and glatiramer acetate cause liver
dysfunction and infusion reaction. Fingolimod may affect the heart, while teriflunomide may cause liver damage. Mitoxantrone is associated with cardiotoxicity (12,15). Although monoclonal antibodies seem to be the most effective approach, the risk of immunogenicity is considered as a problem.

**New Therapeutic approaches**

These include new monoclonal antibodies, combination therapy, vaccination, stem cell treatment, transdermal patch, vitamin D supplements, minocycline, statins, laquinimod and cladribine.

**A. New monoclonal antibodies**

Monoclonal antibodies are becoming a new promising approach for treating patients with MS. Natalizumab is the only FDA approved one. There are three new monoclonal antibodies under study; ocrelizumab, ofatumumab and AIN457 (44).

**Ocrelizumab** is a super-humanized intravenously administered monoclonal antibody working similarly to rituximab. It binds to the CD20 antigen on the surface of B-cells. Ocrelizumab showed reduced brain lesions and relapse rate in a small group of patients with RRMS as well as PPMS. It was associated with mild infusion reaction.

**Ofatumumab** is another super-humanized monoclonal antibody that works similarly to rituximab and ocrelizumab. It is directed against the CD20 antigen. This new drug showed reduced number of lesions when tested on patients with RRMS.

**AIN457** works by binding to interleukin 17 (IL-17). In this way, it reduces recruitment of T-cells. It is being tested for treating patients with RRMS.

**Combination therapy**

Combination therapy is becoming a new approach for MS. Combining glatiramer acetate with β IFNs showed reduced lesions and reduced relapsing rate when compared to either agent alone. Relapsing rate was reduced when the two drugs were combined when compared to IFNs alone. However, monotherapy with glatiramer acetate showed the same relapsing rate and disease progression as the combined therapy (45,46). In terms of disease progression, there were no differences whether these drugs were used together or as monotherapy.

Combining natalizumab and β IFNs has resulted in reduced relapse rate as well as 24% reduction in the progression of the disease (47).

Moreover, add on daclizumab therapy in patients receiving β IFNs showed reduced number of new lesions as indicated by MRI when compared to monotherapy.

**Other approaches**

A number of strategies have been described (44). Vaccines work by decreasing the production of T-cells and also reducing body response to these cells. Stem cells transplantation is another way of treating MS patients but is still under investigation. Myelin peptides have been studied for administration in patients with RRMS through transdermal patches. The results showed reduced relapse, progression and lesions.

Low levels of vitamin D increase the risk of MS. In animal models, vitamin D supplements showed reduced relapse by suppressing T-cells. However, trials on humans have not been conducted. Minocycline is an oral antibiotic that showed immunomodulatory and neuroprotective action.

Simvastain may be beneficial for patients with SPMS; further investigations are needed.

Sphingosine 1-phosphate receptor modulators work in an action similar to fingolimod by altering sphingosine 1-phosphate receptors. There are three new drugs under investigation: siponimod, ponesimod, and ONO-4641. All of them showed promising results.

Laquinimod and cladribine are new immunomodulators. Laquinimod works by a neuroprotective effect, while cladribine showed reduction in relapse rate, progression of the disease, and number of lesions for patients with RRMS.

**Conclusion**

Research in MS is evolving rapidly, but there still remains no cure. A number of disease modifying agents are used to control the disease. Combination therapy of monoclonal antibodies with other agents can reduce relapse rate and generally shows greater efficacy. New therapeutic approaches are also showing promising results. In less than 10 years, a number of new drugs have been developed with proven ability to alter the natural history of MS and mitigate the disease. These advances have completely altered the clinician's approach to the patient with MS and have renewed hope for the ultimate cure of this debilitating disease.
References

1) Which of the following is the only FDA approved monoclonal antibody used in the management of multiple sclerosis?

a) Ocrelizumab  
b) Ofatumumab  
c) Natalizumab  
d) Alemtuzumab  
e) Daclizumab

2) Which of the following is an oral immunomodulator used in MS?

a) beta IFN-1a  
b) beta IFN-1b  
c) Glatiramer acetate  
d) Fingolimod  
e) All of the above

3) Which drug is a sphingosine 1-phosphate receptor modulator that works similar to fingolimod?

a) Laquinimod  
b) Cladribine  
c) Mitoxantrone  
d) Ofatumumab  
e) Ponesimod

Is there a problem?

A 30 year old pregnant patient was prescribed the drug given in the prescription for high cholesterol. Is there any major error?

Answer

Atorvastatin should be avoided in pregnancy.

(Source: British National Formulary)
People with a relatively low socioeconomic status account for a disproportionate number of colorectal cancers in the United States. Now, for the first time, a large prospective, observational study at University of Pennsylvania Perelman School of Medicine in Philadelphia has shed light on the degree to which behaviour and body mass contribute to this disparity.

This study showed that over one third of the excess risk of invasive adenocarcinoma of the colon and rectum resulting from low socioeconomic status could be explained by differences in behavioral risk factors, particularly in an unhealthy diet. In addition to diet, they found that physical inactivity, smoking and being overweight are likely contributors to this risk.

In their study, the authors looked at health behaviours, obesity and colorectal cancer risk among Americans of all socioeconomic statuses. They used the National Institutes of Health-AARP Diet and Health Study as their data source. Specifically, they looked at middle-aged and elderly people from 6 states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, Georgia and Detroit, Michigan). All of the participants enrolled in the study in 1995/96 and were followed through 2006. Health behaviours of the participants were determined using questionnaires. Of the 506,488 study participants, 7676 developed colorectal cancer during the 10-year follow-up period.

Class and behaviour, and body mass
The authors evaluated the socioeconomic status of the participants in 2 ways: by census-tract data, which revealed "neighborhood socioeconomic status," and by self-reported educational level (less than high school vs high school and above). On the basis of data from other studies on colorectal cancer and behaviour, they used statistical modeling to estimate the likely percentage of colorectal cancers mediated by behavioural risk factors. They found that differences in socioeconomic status in the reported levels of physical inactivity, unhealthy diet, smoking, and unhealthy weight each explained between 11.3% and 21.6% of the association between education and risk for colorectal cancer, and between 8.6% and 15.3% of the association between neighbourhood status and risk for colorectal cancer. Diet was found to have the biggest impact of all the health behaviours.

Overall, the combination of health behaviours and body mass index (BMI) explained approximately 43.9% (95% confidence interval [CI], 35.1% to 57.9%) of the association between risk for colorectal cancer and education and 36.2% (95% CI, 28.0% to 51.2%) of the association between the risk and neighbourhood socioeconomic status.

In short, somewhere between one third and nearly one half of colorectal cancers among either low-income or less-than-high-school-educated Americans might be attributable to obesity and unhealthy behaviours. However, some experts not involved with the study, do not find these results to be a cause for despair. Instead, the study "demonstrates the intricate interplay" of socioeconomic and behavioural factors affecting colorectal cancer risk. They believe that public health practitioners can learn from these results. The study underscores the need for more effective public health strategies to improve nutrition and physical activity and thereby curb the rising tide of obesity, particularly for those with less education and in disadvantaged communities.

Colon cancer by location
The study accounted for the anatomic location of the
participants' cancers (proximal colon, distal colon, or rectum). The health behaviours and BMI explained 95% of the association between education and the incidence of proximal colon cancer, but only 38% of the association between education and distal cancer and 24% of that between education and rectal cancer. That is a dramatic difference. However, these contrasting results for proximal and more distal cancers might "reflect the impact of an important omitted variable—colorectal cancer screening by socioeconomic status."

Colorectal cancer screening has been shown to be more effective in reducing cancer incidence and mortality in the distal colon and rectum than in the proximal colon. Thus, this finding might have an easy explanation. Because adults who are less educated and from less affluent communities are less likely to be screened, the greater effectiveness of screening for distal colorectal cancer may explain why socioeconomic gradients were much steeper for these anatomic sites than for proximal cancer.


Combinations of antibiotics and non-antibiotic drugs

Antimicrobial resistance is on the rise, evidenced by greater use of "last resort" antibiotics such as vancomycin and recent epidemics of antibiotic-resistant diseases, including tuberculosis and MRSA.

For decades, researchers and clinicians have been combining antibiotics to increase their efficacy against such resistant bacteria, but those obvious efforts don't go far enough.

So G Wright and his team (Ejim et al, Nature Chemical Biology, doi:10.1038/nchembio.559, 2011) decided to broaden the search. They focused on minocycline, an antibiotic that inhibits protein synthesis, frequently used in the 1950s and 1960s until bacteria developed resistance.

They screened minocycline in combination with more than 1,000 previously approved bioactive drug compounds—most of which had no known antibiotic function—against three common and often resistant bacteria: Pseudomonas aeruginosa, Escherichia coli, and Staphylococcus aureus.

The screen showed that a total of 69 compounds never before used to treat bacterial infections that, when combined with minocycline, decreased bacterial growth by at least 45%—significantly more than when treated with only the antibiotic. One finding that surprised the researchers was that many of the compound combinations inhibited only one of the three bacterial species tested, suggesting that these could be used to target specific infectious bacteria and leave the rest of a patient's microbial flora alone.

The researchers further examined loperamide, an opioid anti-diarrheal agent marketed as Imodium, which inhibited 99% of P. aeruginosa and 70% of E. coli growth when combined with minocycline in the initial screen, though it had no antibacterial function on its own. They found that it disrupts the electron potential across bacterial membranes, effectively weakening the cell and giving the minocycline a way in.

Mark Riddle of the Naval Medical Research Center's Enteric Diseases Department had previously found that treating diarrheal infections with a combination of loperamide and antibiotics resolved patients' symptoms significantly faster. He assumed that this was "likely due to the loperamide helping with the symptoms, while the antibiotics worked on eradicating the infection....But this study opens up the thinking that maybe there are some other mechanisms that it would have in synergising with antibacterial drugs."

Many questions remain, of course, such as how well the drug combinations will be absorbed by the body. But Wright is optimistic that finding new uses for old drugs will give less-effective antibiotics a second wind.
**FDA Reviews and approvals**

In 2010, the FDA published the following reviews, updates and new drug approvals:

**Brand Name Change**
The brand name for dexlansoprazole was changed from KAPIDEX to DEXILANT to avoid name confusion with CASODEX, (bicalutamide).

**Obsolete Indications**
- **Bevacizumab** does not appear to prolong survival or slow disease progression in patients with metastatic breast cancer, so the FDA has proposed withdrawing this indication for the drug.
- **Dolasetron** can increase the risk of torsades de pointes and is no longer recommended for chemotherapy-induced nausea and vomiting.
- **Quinine** can cause life-threatening thrombocytopenia, hemolytic-uremic syndrome, and thrombotic thrombocytopenic purpura. Quinine is no longer recommended for the off-label use for leg cramps.

**Marketed unapproved drugs**
FDA granted market approval to 2 previously unapproved marketed drugs. The newly licensed versions are morphine sulfate oral solution concentrate (20 mg/ml) and pancrelipase (PANCREAZE).

**Market withdrawals/suspensions**
- **Gemtuzumab** a monoclonal antibody, was withdrawn from the US market due to a lack of survival benefit for patients with acute myeloid leukemia. Generic manufacturers have been informed of FDA’s recommendation for healthcare professionals to stop prescribing the drug.
- **Propoxyphene** was withdrawn from the US market due to evidence of risk for serious heart rhythm abnormalities.
- **Rosiglitazone** has been suspended from marketing in Europe and placed on a restricted distribution status in the US due to increased cardiovascular risk.
- **Sibutramine** was withdrawn from the US market due to increased risks for heart attack and stroke associated with its use for weight loss.

**Updates**
- Tamper-resistant OxyContin (oxycodone) formulation: is intended to prevent the medication from being cut, broken, chewed, crushed or dissolved to release medication more rapidly than intended.
- Update on the Clinical Impact of USP Heparin Potency Reduction: The 10% decrease in anticoagulation activity of heparin products manufactured under the USP standard may warrant adjustments in heparin dosage and monitoring in the following situations: i), extracorporeal membrane oxygenation in pediatric patients, ii), cardiopulmonary bypass, and iii), treatment or prevention of life-threatening thrombosis.

**“Re-purposed” drugs**
Four established drugs were approved for new purposes or as novel formulations for established purposes.

**Licensed vaccines and biologies**
- A photodynamic imaging agent, hexaminolevulinate hydrochloride (CYSVIEW), was licensed for the detection of superficial bladder cancer during cystoscopy.
- Human papillomavirus (HPV) vaccine (Gardasil) licensure was extended for children and young adults aged 9 to 26 years to include the prevention of anal cancer and associated precancerous lesions due to HPV types 6, 11, 16, and 18.
- A fourth alpha1-proteinase inhibitor (Glassia) was licensed for treatment of emphysema due to congenital deficiency of alpha1-antitrypsin.
- A new 13-valent pneumococcal conjugate vaccine (Prevnar 13) was licensed to prevent invasive pneumococcal disease and otitis media in children aged 6-weeks to 5-years old.
- The first RANK ligand inhibitor, denosumab (PROLIA, XGEVA), was licensed for prevention of
skeletal fractures and pain in patients with bone metastases from solid tumors (XGEVA) and for postmenopausal osteoporosis (PROLIA).

- An autologous cellular immunotherapy, sipuleucel-T (PROVENGE) was licensed for the treatment of metastatic hormone-refractory prostate cancer.
- An absorbable fibrin sealant patch (TACHOSIL) was licensed for use as an adjunct to hemostasis in cardiovascular surgery when control of bleeding by suture, ligature or cautery, is ineffective or impractical.
- Velaglucerase alfa (VPRIV), a glucocerebroside-specific enzyme, was licensed for long-term replacement treatment of type 1 Gaucher disease.

**Anticancer agent derived from marine invertebrates**

- Eribulin (HALAVEN), an antimitotic indicated for breast cancer, is the first drug derived from the sea sponge, Halichondria okadai.

**Orphan drugs**

- Carglumic acid (CARBAGLU) is an analogue of N-acetylglutamate (NAG). NAG is the product of N-acetylglutamate synthase (NAGS). NAGS deficiency is a very rare genetic disorder characterized by hyperammonemia, encephalopathy, and respiratory alkalosis, and is frequently fatal within the first days-to-hours after birth. Carglumic acid is used to decrease the frequency of hyperammonemic crises and reduces the associated neurotoxicity. Concomitant therapy with other ammonia lowering strategies is recommended.
- Collagenase clostridium histolyticum (XIAFLEX) is used to treat Dupuytren disease. Up to three repeat injections per palpable cord may be administered if needed. Common side effects are: tendon ruptures, pain, swelling, bruising, and bleeding at the injection site, hypersensitivity reactions and risk of fainting during the post-injection finger extension procedure.

**“First in class” medicines**

- Fingolimod (GILENYA) is the first oral medication for multiple sclerosis marketed in the US. It is superior over interferon beta-1a over the course of 12 months of study. Side effects include: bradycardia, heart block, immunosuppression, lymphoma, serious infection, macular edema, change in visual acuity, reduction in pulmonary function, hepatic dysfunction, hypertension and hepatotoxicity. Women of childbearing potential should use effective contraception to avoid pregnancy during, and extending for 2 months after its discontinuation. Untoward reactions may also occur in patients receiving antiarrhythmic drugs, beta-blockers, calcium channel blockers, antihypertensive drugs, drugs for heart failure, ketoconazole, live attenuated vaccines, antineoplastics, immunosuppressives, immune modulators, and antigenic testing concurrently with fingolimod and for up to 2 months after its discontinuation. The recommended dose of fingolimod is 0.5 mg orally once daily. Patients should have baseline laboratories drawn before starting therapy and should be monitored for bradycardia for 6 hours after the first dose.
- Tesamorelin (EGRIFTA) is a GHRH analog approved for reducing visceral adipose tissue in patients with HIV-associated lipohypertrophy. Tesamorelin is administered subcutaneously once daily. The drug is contraindicated in patients with disruption of the hypothalamic-pituitary axis, active malignancy, and during pregnancy. Adverse effects include fluid retention, hemoglobin A1c elevation, glucose intolerance, development of diabetes, injection site reactions, and hypersensitivity reactions. Tesamorelin induces growth hormone secretion from the pituitary which results in insulin-like growth hormone 1 secretion from the liver and peripheral tissues.

Careful monitoring of patients receiving concomitant therapy with CYP450 substrates is warranted, particularly patients receiving chronic corticosteroids and glucocorticoids. The reduction was sustainable for up to a year of treatment with regain of the fat lost upon its discontinuation. The magnitude of fat loss with tesamorelin is similar to diet and exercise.

- Tocilizumab (ACTEMRA) is the 9th immunomodulator approved for rheumatoid arthritis. It is the first-in-class anti-interleukin 6 (IL-6) receptor monoclonal antibody. Tocilizumab is indicated for once-a-month intravenous infusion, with or without methotrexate, for patients who have failed therapy with one or more TNF antagonists. Adverse effects include: infusion reactions, development of neutralizing antibodies, hypersensitivity reactions, elevation of the risk for serious infections and reactivation of latent infections, and risk of malignancy, hyperlipidemia, gastrointestinal perforation, and symptoms of demyelinating disorders.

Tocilizumab may result in a shift in the expression
of hepatic CYP450 enzymes and may lead to clinically significant drug interactions with narrow therapeutic index substrates of these isozymes. Decrease in rheumatoid factor, erythrocyte sedimentation rate and serum amyloid A levels but increase in hemoglobin values are noted. Its half-life for elimination is 11-12 days. Tocilizumab is the first biologic to demonstrate superiority over methotrexate.

- **Ulipristal (ELLA)** is the first progesterone receptor modulator with antagonist and partial agonist effects. Ulipristal is approved as a 30 mg single-dose emergency contraceptive. Ulipristal is only available by prescription and can be taken up to 5 days after unprotected intercourse. Common adverse reactions are: headache, abdominal pain, nausea, dysmenorrhea, fatigue, dizziness, and a one-time disruption to the menstrual cycle length. Ulipristal may reduce the efficacy of regular hormonal contraceptives. It is metabolized by CYP3A4 to mono- and di-demethylated metabolites. Its mechanism of action is ovulation delay or inhibition.

**Self subscribing for patients?**

### Prescription and non-prescription drugs

Under the Federal Food, Drug, and Cosmetic Act (FD Act), the US FDA approves new drugs either as prescription or non-prescription. A drug must be dispensed by prescription if, “because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, it is not safe for use except under the supervision of a practitioner licensed by law to administer such drug.” FDA has considerable latitude in determining whether the information submitted as part of a new drug application (NDA) is sufficient to ensure that a drug is safe for use under its proposed labeling. FDA also makes a determination under as to whether the product meets the criteria for prescription-only dispensing.

Prescription drugs are dispensed upon receipt of a prescription from a practitioner licensed by law to administer the drug (which may include health care professionals such as physicians, nurse practitioners, physician's assistants, and others whom we will refer to here as practitioners or prescribers). In many instances, a patient has to obtain at least the initial prescription, and in some cases, prescription refills, from a practitioner through an in person interaction. Obtaining a refill for other prescription drugs involves at least a telephone call or other communication with the practitioner. In contrast, non-prescription drugs (OTC products) can be purchased by consumers in pharmacies, supermarkets, and other retail establishments without the need for a prescription.

Currently, consumers can purchase non-prescription drugs from a retailer for diseases or conditions that do not meet the statutory criteria for prescription products and that are safe and effective for use in self-medication as directed in the labeling. Generally, OTC products: 1), are available to treat diseases or conditions that can be self-diagnosed without a prior interaction with a practitioner, 2), are not associated with toxicities that require an evaluation of the benefits and risks by a practitioner; and 3), do not require a practitioner's input for use.

### Under-treatment of diseases and other effects on the health care system

Under-treatment of many common diseases or conditions in the US is a well recognised public health problem. Increasing the number of people who are able to obtain for the first time and those who continue on necessary drug therapy could provide improved health outcomes.

The requirement to obtain a prescription for appropriate medication (and to make one or more visits to a practitioner) may contribute to under-treatment of certain common medical conditions including hyper-
lipidemia (high cholesterol), hypertension (high blood pressure), migraine headaches, and asthma.

For instance, some consumers do not seek necessary medical care, which may include prescription drug therapy, because of the cost and time required to visit a health care practitioner for an initial diagnosis and an initial prescription. Some patients who obtain an initial prescription do not continue on necessary medication because they would need to make additional visits to a health care practitioner for a prescription refill after any refills authorized by the initial prescription have been used or the time during which they can be filled has expired. Some prescription medications require routine monitoring through the prescribing practitioner such as blood tests to assist in the diagnosis of a condition, or to determine whether or how well the medication is working, or to adjust the dose.

FDA believes that some of these visits could be eliminated by making certain prescription medications available without a prescription but with certain other conditions of safe use that would ensure they could be used safely and effectively without the initial involvement of a health care practitioner. In some cases, a visit to a practitioner would be required for the initial prescription, but a certain number of refills could be authorized beyond those that would normally be authorized without a return visit under specialized conditions of safe use. This paradigm might be useful for certain rescue medicines, such as inhalers used to treat asthma or epinephrine for allergic reactions, that patients need to keep on hand for use in emergencies.

In addition to improved health outcomes for consumers staying on their medications, the time and attention that physicians and other health care providers expend on routine tasks related to prescription refills reduces the time that they are available to attend to more seriously ill patients. Eliminating or reducing the number of routine visits could free up prescribers to spend time with more seriously ill patients, reduce the burdens on the already overburdened health care system, and reduce health care costs.

**New paradigm**

FDA is considering whether medications for certain diseases or conditions that would otherwise be available only by prescription could be made available without a prescription with certain conditions of safe use. For example, some conditions of safe use could be designed to assist patients in self-selection of an appropriate medication or provide for follow-up monitoring during continued use. The conditions of use could include requiring pharmacist intervention to ensure appropriate nonprescription use. Additionally, conditions of safe use could involve the use of innovative technologies, such as diagnostics approved or cleared by FDA for use in the pharmacy or other setting.

FDA is aware that industry is developing new technologies that consumers could use to self-screen for a particular disease or condition and determine whether a particular medication is appropriate for them. For example, kiosks or other technological aids in pharmacies or on the Internet could lead consumers through an algorithm for a particular drug product. Such an algorithm could consist of a series of questions that help consumers properly self-diagnose certain medical conditions, or determine whether specific medication warnings contraindicate their use of a drug product. In addition, for some drug products that require an initial prescription, the product could be made available as a nonprescription product with a condition of safe use for the purpose of product refills.

In addition, some drug products that would otherwise require a prescription could be approved as nonprescription drug products with some type of pharmacist intervention as their condition of safe use. For example, some diseases or conditions might require confirmation of a diagnosis or routine monitoring using a diagnostic test (e.g., a blood test for cholesterol levels or liver function) that could be available in a pharmacy. A pharmacist, or consumer, could then use the results to determine whether use of a certain drug product is appropriate.

Other potential roles for the pharmacist include assessing whether the consumer has any conditions or other risk factors that would indicate that the drug
Researchers at the Immunobiology laboratory at Massachusetts General Hospital in Boston conducted a small trial of a vaccine that has already been approved for tuberculosis and found that the vaccine can kill the autoimmune cells that are active players in type 1 diabetes. There were no changes however, in the need for insulin among those with longstanding diabetes who received the vaccine.

Two vaccines, given four weeks apart, caused the death of bad T-cells according to the study author. They found that the good regulatory T-cells came on and the pancreas went on briefly. This was in people who were 15 years out from their type 1 diagnosis. This doesn't mean that people were discarding their insulin syringes. But the exciting part of this study is that even decades after the disease begins, the cells in the pancreas can regain function albeit briefly.

The vaccine, which has been approved by the U.S. FDA, is called bacille Calmette-Guerin (BCG), and has been used against tuberculosis for about 90 years.

BCG also is used as a treatment for bladder cancer. The vaccine works by increasing levels of tumor necrosis factor (TNF). High doses of TNF can be toxic, but the vaccine doesn't appear to raise levels of TNF too high. According to the U.S. Centers for Disease Control and Prevention, the only groups that shouldn't receive the live vaccine are those whose immune systems are compromised, such as people who have HIV or people who have received an organ transplant. The CDC also recommends against giving the vaccine to pregnant women because it hasn't been well-studied in this population.

In 2001, this team tested a similar substance in mice and found that it destroyed the harmful T-cells and allowed the insulin-producing cells in the pancreas to regenerate and produce insulin. They then wanted to know if such regeneration can take place to demonstrate that certain drugs could be used safely and effectively in the nonprescription setting with conditions of safe use. Depending upon the situation, applications for approval of non-prescription products with conditions of safe use may need to include patient studies (e.g., self-selection studies, label comprehension studies, and actual use studies) to demonstrate that the drug would be safe and effective under the specified conditions. When a device, e.g., diagnostic test or computer algorithm, is necessary as a condition of safe use, evidence may need to be submitted demonstrating that it will perform its intended function and can be appropriately administered in the particular setting in which it will be used. Certain classes of drugs may be appropriate candidates for non-prescription use under this new paradigm, but FDA would need to evaluate each NDA.

Source: https://www.federalregister.gov/articles/2012/02/28/2012-4597/using-innovative-technologies-and-other-conditions-of-safe-use-to-expand-which-drug-products-can-be
in humans with type 1 diabetes if the immune-system attack that causes type 1 diabetes in the first place was stopped. To answer that question, they recruited six people with type 1 diabetes who were randomly assigned to receive two injections of either the vaccine or a placebo, and they were compared to one control group without diabetes and one with the disease. The average duration of type 1 diabetes at the beginning of the study was 15.3 years, and the average age of those with diabetes was 35. During the 20-week study, two out of the three people treated with BCG had evidence of bad T-cell death and increases in the levels of protective T-cells. They also showed an elevation in levels of a substance called C-peptide that indicates insulin production. It was not clear why BCG didn't appear to help one of those treated with it, but at the end of the study, the individual's level of C-peptide began to increase.

It's not yet certain whether more frequent doses or higher doses would be needed to restore more pancreatic function, but it may matter how long someone has had the disease.

However, according to the authors, no matter how long someone has had the disease, they'll likely get some function back. Any restoration of C-peptide helps to prevent diabetes complications.

One expert said the finding was important, but many questions remain. This study shows that by increasing TNF, they can induce the death of the auto-reactive T-cells that destroy the cells that make insulin, and they transiently increase C-peptide levels - but what happens after 20 weeks? Another question is how often would they need to give this vaccine? Some experts are also concerned about whether increasing the levels of TNF in the body may have long-term effects, if it's given repeatedly. Some would like to know whether this could be used in children.

However, experts believe that this is an important research that will help in the understanding of the pathophysiology of type 1 diabetes.

BCG has an excellent safety record, and has been given to billions of adults and children worldwide to prevent tuberculosis. The authors of the study are currently developing phase II trials to test using higher levels of the vaccine.